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THE USE OF ANTIMALARIAL DRUGS

Report of a WHO Informal Consultation

13–17 November 2000

World Health Organization

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CONTENTS

ABBREVIATIONS

ACR	adequate clinical response
ACT	artemisinin-based combination therapy
AIDS	acquired immunodeficiency syndrome
AQ	amodiaquine
ART	artemisinin
ASU	artesunate
AT	atovaquone
ATM	artemether
AUC	area under curve (time–concentration)
C_{max}	maximum plasma concentration
CD	clindamycin
CNS	Central Nervous System
CQ	chloroquine
CT	combination therapy
D	doxycycline
DHFR	dihydrofolate reductase
DHPS	dihydropteroate synthetase
EANMAT	East African Network for Monitoring Antimalarial Treatments
ETF	early treatment failure
GI	Gastro-intestinal
G6PD	glucose-6-phosphate dehydrogenase
HAL	halofantrine
HIV	human immunodeficiency virus
HPLC-ECD	high-performance liquid chromatography-electron capture detection
LTF	late treatment failure
LUM	lumefantrine
MQ	mefloquine
P. falciparum	*Plasmodium falciparum*
P. ovale	*Plasmodium ovale*
P. malariae	*Plasmodium malariae*
P. vivax	*Plasmodium vivax*
PAHO	Pan American Health Organization
PQ	primaquine
Q	quinine
RDT	rapid diagnostic test
SP	sulfadoxine–pyrimethamine
T	tetracycline
WHO	World Health Organization

INTRODUCTION

The WHO Informal Consultation on the Use of Antimalarial Drugs was held from 13 to 17 November 2000 in Geneva, Switzerland. The participants reflected a broad range of expertise in the development and use of antimalarial drugs, and in the implementation and adaptation of antimalarial treatment policies (see Annex 1 for List of participants).

Early diagnosis and prompt treatment are fundamental components of the WHO global strategy for malaria control (1). Correct use of an effective antimalarial drug will not only shorten the duration of malaria illness but also reduce the incidence of complications and the risk of death. Antimalarial drug resistance has spread and intensified over the last 15–20 years (2–4), however, leading to a dramatic decline in the efficacy of the most affordable antimalarial drugs. Development of new drugs is not keeping pace (5), and problems related to the distribution and use of these drugs have compounded the situation. In many malarious areas, a majority of the population does not have ready access to antimalarial drugs and to reliable and consistent information about malaria treatment and prevention (6). Moreover, those drugs that are available are frequently obtained from informal sources and may be counterfeit; they are of variable quality, may be partially or completely ineffective against local parasite strains, and are often used in inappropriate dosages (7).

Many endemic countries are beginning to face a situation in which there are no affordable, effective antimalarial drugs available. Combination therapy offers hope for preserving the efficacy of antimalarial drugs and prolonging their useful therapeutic life (8–11), although it may not necessarily provide better treatment for consumers. The development of artemisinin and its derivatives—the most rapidly acting of all the current antimalarial drugs—and recognition of their potential role as a component of combination therapy (8, 9, 12, 13) have led to several large trials aimed at assessing different combinations of existing drugs, and to the specific development of new combination drugs. In addition, several countries have felt the need to evaluate, as potential first-line treatments, drug combinations that do not include artemisinin. These changes have provided an impetus for updating and rationalizing antimalarial treatment policies.

National antimalarial treatment policies are essential to provide countries with a framework for the safe and effective treatment of uncomplicated and severe malaria as well as for the prevention of malaria in travellers and in vulnerable groups, such as pregnant women and young children. As a general principle, such policies should aim at the greatest possible reduction of malaria mortality and morbidity, while containing the development of resistance and remaining compatible with limited national health budgets and health care infrastructures. All health care providers in both the public and private health sectors must be aware of, understand the rationale for, and implement the national policy. Such national policies should be updated to take account of the development of antimalarial drug resistance in the country. A framework for this purpose has been developed for use in Africa (14).

The treatment of severe malaria is covered comprehensively in the *Transactions of the Royal Society of Tropical Medicine and Hygiene* supplement Severe falciparum malaria (15). The use of antimalarial drugs for chemoprophylaxis and the prevention and treatment of uncomplicated malaria was last reviewed at a WHO informal consultation in September 1995 (16), which also considered diagnosis and the principles of clinical management. Since then, considerable additional experience has been gained in the use of existing and new antimalarial drugs, alone and in combination.

In view of the new evidence available on malaria prevention and treatment and on the further spread of resistance to antimalarial drugs, WHO considered it timely to convene an informal consultation to:

- review and update recommendations on the use of antimalarial drugs for malaria prevention and the treatment of uncomplicated malaria;
- assess the implications of the latest drug developments for national antimalarial treatment policies.

The informal consultation took the form of presentations of prepared papers, followed by discussions during which specific conclusions and recommendations were agreed. The proceedings of the consultation and the working papers form the basis of this report.

The report is aimed at managers of national malaria control programmes and those involved in implementing antimalarial treatment policies. Part I provides information on the current status of antimalarial resistance throughout the world, considers the potential for combination therapy, updates recommendations on the prevention and treatment of malaria in specific target groups, and outlines the development and implementation of an antimalarial treatment policy. Part II describes the antimalarial drugs and recommended regimens in current use for malaria prevention and for the treatment of uncomplicated malaria. It also covers antimalarial drugs under development. The report also presents options for different treatment scenarios according to specific epidemiological situations. Individual countries will need to adapt the recommendations made in this report to their own epidemiological and health care context.

PART I

POLICY IMPLICATIONS

1. CURRENT STATUS OF ANTIMALARIAL DRUG RESISTANCE

1.1 Development of resistance

Antimalarial drug resistance is the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the subject (17).

Resistance to antimalarial drugs arises as a result of spontaneously-occurring mutations that affect the structure and activity at the molecular level of the drug target in the malaria parasite or affect the access of the drug to that target (18). Mutant parasites are selected if antimalarial drug concentrations are sufficient to inhibit multiplication of susceptible parasites but are inadequate to inhibit the mutants, a phenomenon known as "drug selection" (11, 19). This selection is thought to be enhanced by subtherapeutic plasma drug levels and by a flat dose–response curve to the drug.

The evolution of drug resistance in Plasmodium is not fully understood although the molecular basis for resistance is becoming clearer. The development of resistance to chloroquine probably requires successive gene mutations and evolves slowly. Recent evidence indicates that for *P. falciparum* some of these mutations occur in a transporter-like gene on the surface of the parasite food vacuole (20). Preliminary reports suggest that a different set of mutations is probably involved in chloroquine resistance for *P. vivax* (20). The molecular basis for resistance to antifolates, such as sulfadoxine–pyrimethamine has been well characterized. *P. falciparum* resistance to sulfadoxine–pyrimethamine is primarily conferred by successive single-point mutations in parasite *dhfr,* the gene that encodes the target enzyme dihydrofolate reductase (DHFR), and by additional mutations in *dhps*, which encodes for the enzyme dihydropteroate synthetase (DHPS) (21).

Various factors relating to drug, parasite and human host interactions contribute to the development and spread of drug resistance. The molecular mechanism of drug action is a critical element in the speed at which resistance develops. In addition, drugs with a long terminal elimination half-life enhance the development of resistance, particularly in areas of high transmission. Similarly, increased drug pressure is a significant contributor to drug resistance. As increased amounts of a drug are used, the likelihood that parasites will be exposed to inadequate drug levels rises and resistant mutants are more readily selected (22). Parasite factors associated with resistance include the Plasmodium species concerned and the intensity of transmission. Human host factors include the widespread and/or irrational use of antimalarial drugs and possibly the level of host immunity. The role of host immunity in propagating resistance is unclear. However, immunity acts synergistically with chemotherapy and can enhance therapeutic effects and even parasite clearance of drug-resistant infections.

The increase in chloroquine resistance in East Africa has led to a rise in malaria mortality (4). Similarly, a significant rise in malaria mortality in children under 5 years of age has been obseved in Senegal in West Africa, coinciding with the emergence of chloroquine resistance in the area (23). The incidence of severe malaria has risen with increasing chloroquine resistance in

Malawi and Democratic Republic of the Congo (24). Antimalarial drug resistance has also been implicated in the increasing frequency and severity of epidemics (3).

Conditions for the development and spread of drug resistance differ between the Asian and African continents. Migration of individuals carrying resistant gametocytes has probably been of major importance for the spread of chloroquine resistance between different endemic areas in Asia and Oceania and the initial introduction of chloroquine resistance to East Africa.

1.2 Assessment of antimalarial drug susceptibility

Parasite susceptibility to antimalarial drugs can be assessed by *in vitro* or *in vivo* techniques. *In vitro* techniques rely on the collection of parasitized blood from patients and the testing of parasite susceptibility to drugs in culture or by the use of molecular techniques such as PCR. *In vivo* techniques rely on monitoring of the symptoms associated with malaria, such as fever, and parasitaemia (25).

A major purpose of assessing the therapeutic efficacy of antimalarial drugs in confirmed malaria patients is to monitor efficacy over time, especially in vulnerable groups in highly endemic areas, and to guide treatment policy. Antimalarial drug responses are assessed clinically from rates of symptom resolution e.g. fever clearance, coma recovery, or parasitologically from parasite clearance and overall cure rates.

Until the end of the 1980s, most *in vivo* studies focused on the parasitological response to a given drug, and infections were classified as sensitive (S), or resistant (R) at one of three levels, RI, RII or RIII. An RI response corresponds to an initial clearance of parasitaemia and then recrudescence 8 or more days after treatment; an RII response is the clearance or substantial reduction of parasitaemia with recrudescence of parasitaemia on day 7; and an RIII response refers to a situation in which there is no initial reduction of asexual parasitaemia and the levels may actually increase (17). Follow-up of treated patients for evidence of recurrence of parasitaemia may continue for 7, 14 or 28 days, depending on the investigators' interest in detecting lower levels of resistance and on budgetary limitations (26–28).

Protocols have been modified and simplified to facilitate their use in high-transmission areas in Africa, where populations may have asymptomatic parasitaemia in the absence of clinical manifestation. The generally accepted objective of malaria treatment in these areas is not so much the clearance of parasitaemia but the resolution of clinical symptoms and acute febrile illness as measured by the adequate clinical response (ACR) and early and late treatment failure (ETF and LTF) (29). The therapeutic response is classified as ETF if the patient develops clinical or parasitological symptoms during the first 3 days of follow up; and as LTF if the patient develops symptoms during the follow-up period from day 4 to day 14, without previously meeting the criteria for ETF. ACR is defined as either the absence of parasitaemia on day 14 (irrespective of axillary temperature), or the absence of clinical symptoms on day 14 (irrespective of parasitaemia), in patients who did not meet the criteria of ETF or LTF before. Although the measurement of clinical response is of value in areas of high transmission, the impact of asymptomatic residual parasitaemia on other malaria-related conditions, such as anaemia and malnutrition, has not been examined (2).

WHO has further adapted a protocol for use in areas with moderate or low endemicity (large areas in South-East Asia, the Western Pacific region, the Eastern Mediterranean region, South America and Central America, and parts of tropical Africa) using the same classification.

However, in these areas, the objective of malaria treatment is the clearance of the parasitaemia as well as the resolution of clinical symptoms.

Experience in malaria control programmes has shown that *in vitro* tests of parasite susceptibility to antimalarial drugs cannot substitute for *in vivo* observations on malaria therapy. However, they are a useful research tool to provide background information for the development and evaluation of drug policies and can provide an early warning of the appearance of drug resistance. They are best used to define specific aspects of the temporal and geographical response to drugs: longitudinal follow-up of drug susceptibility of the parasites in areas where changes are introduced compared with those where such changes are not implemented; longitudinal follow-up of susceptibility to a drug previously withdrawn because of an unacceptable level of resistance; monitoring of cross-resistance patterns; and the establishment of baseline data on responses to a new antimalarial drug prior to its deployment for treatment. The application and usefulness of *in vitro* tests is restricted by the need for trained personnel and their labour-intensive nature.

1.3 *Plasmodium falciparum* resistance

A global picture of reduced susceptibility of *P. falciparum* to various antimalarial drugs is provided in figure 1.

Chloroquine

Strains of *P. falciparum* resistant to chloroquine were first suspected in Thailand in 1957 and found in patients in Colombia and Thailand in 1960. Since then, resistance to this drug has spread widely and there is now high-level resistance to chloroquine in South Asia, South-East Asia, Oceania, the Amazon Basin and some coastal areas of South America. In Africa, chloroquine resistance was first documented in the United Republic of Tanzania in 1979 and has spread and intensified in the last 20 years. In most countries of East Africa and in Ethiopia more than 50% of patients currently experience a recurrence of parasitaemia with symptoms by day 14 after treatment. Moderate levels of resistance are found in central and southern Africa. In West Africa, reported rates of resistance vary widely but tend to be lower than in central and southern Africa. Strains of *P. falciparum* remain sensitive to chloroquine in Central America north of the Panama Canal, the island of Hispaniola (Haiti and the Dominican Republic) and in El Faiyûm governorate in Egypt.

Amodiaquine

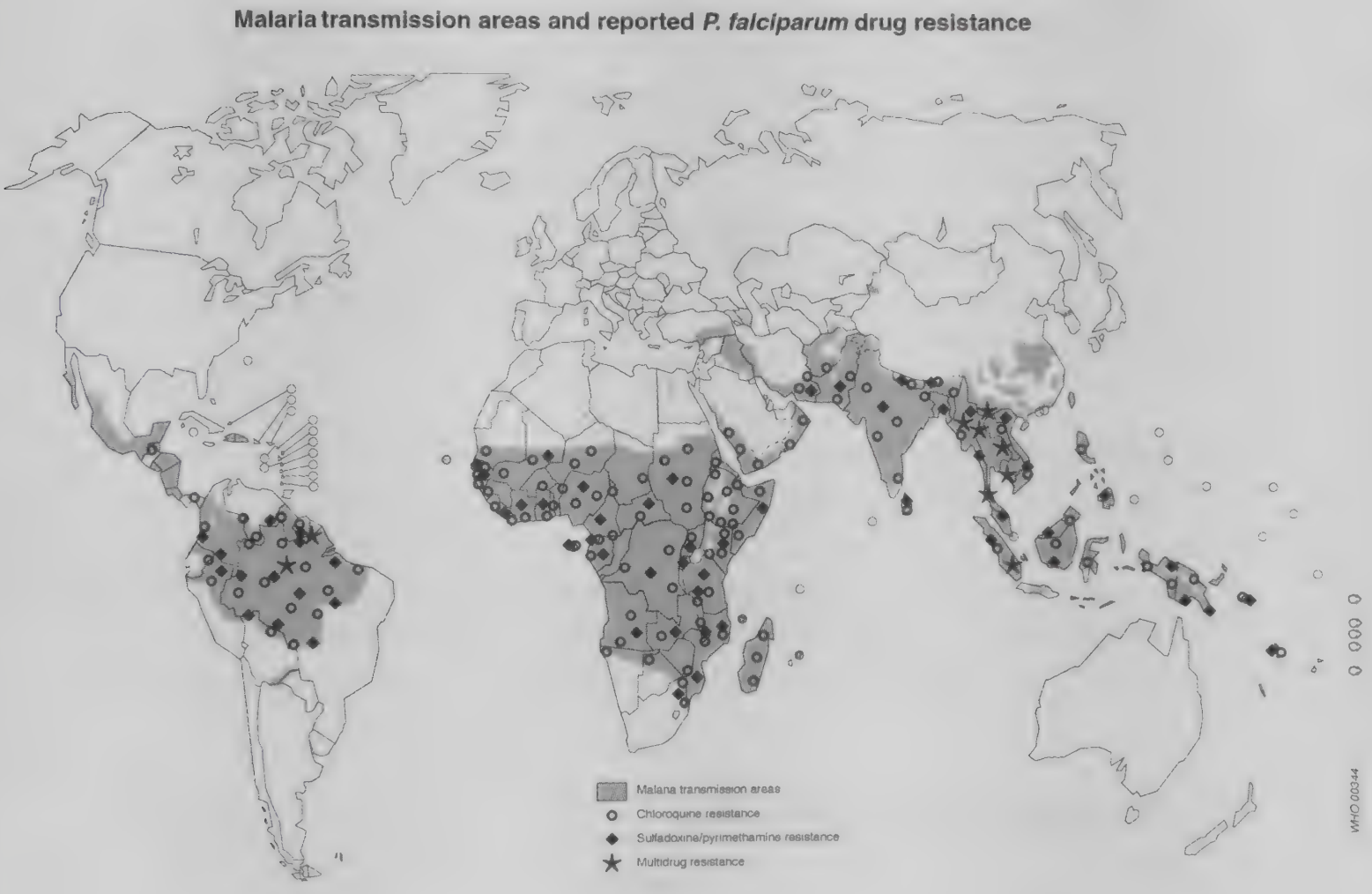
Although amodiaquine is generally more effective than chloroquine against chloroquine-resistant strains of *P. falciparum* (30), there is cross-resistance and moderate-to-high levels of amodiaquine resistance have been reported from Papua New Guinea, East Africa and the Amazon Basin. This drug continues to be efficacious as a single drug in most of West and central Africa and on the northern Pacific Coast of South America where, in some countries, it is used in combination with sulfadoxine–pyrimethamine.

Sulfadoxine–pyrimethamine

High levels of resistance to this drug are found in the Amazon Basin and throughout South-East Asia, with the possible exception of some areas in eastern Cambodia and northern Viet Nam. In East Africa resistance rates are variable, ranging from 10–50% in 14-day therapeutic

efficacy trials. Low levels of resistance (< 10% ETF + LTF) are found on the Indian subcontinent, in central and southern Africa and in coastal areas of South America.

Fig. 1. Reduced susceptibility of *Plasmodium falciparum* to various antimalarial drugs (from published and unpublished sources using a variety of criteria)



Quinine

Decreasing sensitivity to quinine has been detected in areas of South-East Asia where it has been extensively used as the first-line treatment for malaria and in some parts of South America. Patient adherence to a 7-day regimen as a single drug or in combination with other drugs such as tetracyclines is low, leading to incomplete treatment and parasite recrudescences. This may have led to the selection of resistant parasites. There is some cross-resistance between quinine and mefloquine, suggesting that the wide use of quinine in Thailand might have influenced the development of resistance to mefloquine in that country (31). Strains of *P. falciparum* from Africa are generally highly sensitive to quinine.

Mefloquine

Recurrences of parasitaemia in over 50% of the patients treated with mefloquine alone have been reported from border areas between Cambodia, Myanmar and Thailand. Mefloquine resistance is uncommon in the remainder of South-East Asia. In the Amazon Basin, mefloquine resistance has been reported only from Brazil, where clinical failure rates remain below 5% (32). Existing data indicate that, in some endemic areas, mefloquine-resistant parasites may be found prior to the introduction of the drug. For example, isolates with reduced sensitivity to mefloquine have been reported from several sites in West and central Africa, although the drug has never been widely used there (33). In such cases, there is a potential for resistance to spread if mefloquine monotherapy is used on a large scale.

Artemisinin and its derivatives

The recrudescence rate is high when these drugs are used in monotherapy, depending on the dose administered, the duration of treatment and the severity of disease but not at present on parasite resistance (34–38). Treatment regimens of less than 7 days gave unacceptably high recrudescence rates (39). In spite of reports of decreasing in vitro susceptibility so far, there is no confirmed *in vivo* evidence of resistance of *P. falciparum* to artemisinin and its derivatives.

1.4 *Plasmodium vivax* resistance

Chloroquine

P. vivax resistance to chloroquine was first reported from Irian Jaya (Indonesia) and Papua New Guinea in 1989. Nearly 50% of strains from these areas currently show evidence of reduced susceptibility in 28-day *in vivo* tests (40). Well-documented reports of resistance in individual patients or small case series have also appeared from Brazil, Guatemala, Guyana, India and Myanmar but the resistance appears to be focal and much less intense.

1.5 Regional responses to antimalarial drug resistance

Africa

The current situation is summarized in Table 1. Since 1995, WHO and national malaria control programmes in the African Region have responded to the spread and intensification of chloroquine-resistant *P. falciparum* by strengthening national capacity in conducting 14-day *in vivo* drug efficacy studies in more than 30 countries south of the Sahara.

Table 1. Emergence of resistance to antimalarial drugs and antimalarial treatment policies in selected African countries[a]

Country	Drug for which reduced susceptibility of parasite reported (year of reporting if known)	Current first-line policy (November 2000)	Current second-line policy
Botswana	CQ (1984)	SP	Q
Kenya	CQ (1979) SP (1998)	SP	AQ
Ethiopia	CQ (1987)	CQ + SP (if no microscopy available, otherwise CQ for *P. vivax* and SP for *P. falciparum*)	Q
Ghana	CQ (1987) SP	CQ	SP
Malawi	CQ (1984)	SP	Q
Mali	CQ SP	CQ	SP
South Africa	–	SP	Q
Uganda	–	CQ + SP	Q
United Republic of Tanzania	CQ (1978) SP (1982)	SP	AQ
Zambia	CQ (1978)	CQ (new recommendation is SP but not officially adopted)	

AQ, amodiaquine; CQ, chloroquine; Q, quinine; SP, sulfadoxine–pyrimethamine

[a] In countries not listed in the table, chloroquine is used as first-line and sulfadoxine–pyrimethamine as second-line drug treatment.

On the basis of the results from these studies, as of date nine countries have changed their antimalarial treatment policies: Botswana, Ethiopia, Kenya, Malawi, South Africa, Uganda, United Republic of Tanzania, Zambia and Zimbabwe. Burundi, Eritrea, Ghana, Mozambique, Rwanda and Zambia have started the process of change. In West Africa, rates of resistance vary, but tend to be lower than those in East and southern Africa and as yet no changes have been made in first-line treatment policy.

Asia

As shown in Table 2, chloroquine resistance was suspected in Asia as early as 1957. Chloroquine and sulfadoxine–pyrimethamine resistance are widespread in some parts of Cambodia, Lao PDR, Malaysia, Myanmar, Thailand and Viet Nam. In areas of sulfadoxine–pyrimethamine resistance, mefloquine has been the drug of choice. However, mefloquine resistance has spread rapidly in this region. In response, following a regional meeting of the Mekong Roll Back Malaria Initiative in May 2000, a standard of combination therapy including an artemisinin derivative was adopted for use following diagnosis by microscopy or rapid diagnostic testing. In this region, malaria is most prevalent in border areas; malaria control collaboration efforts therefore include antimalarial treatment policies. Combinations of quinine plus tetracycline or artemisinin derivatives plus mefloquine are being used. In western Cambodia,

mefloquine resistance was first identified in 1995. The current policy is artemisinin combination therapy with mefloquine. Combination therapy is also being considered in the Philippines. One of the challenges to combination drug policy is that there are currently no formulations of the recommended combinations for use in children or during pregnancy.

Table 2. Emergence of resistance to antimalarial drugs and antimalarial treatment policies in selected Asian countries

Country	Drug for which reduced susceptibility of parasite reported (year of reporting if known)	Current first-line policy (November 2000)	Current second-line policy
Afghanistan	CQ	CQ	SP
Bangladesh	CQ (1970) SP (1985)	CQ + PQ (*P. vivax*: CQ)	Q-3 + SP or Q-7
Bhutan	CQ (1985) SP (1990)	ASU or ATM (laboratory confirmed) (*P. vivax*: CQ)	ATM + Q
Cambodia	CQ (early 1960s) SP (late 1960s) MQ (1995)	CQ (limited areas) ASU-3 + MQ (20 mg/kg) (following RDT in other areas)	Q-7 + T-7
India	CQ (1973) SP (1979) *P. vivax* resistance to CQ (1991)	CQ (25 mg/kg) + PQ (*P. vivax*: CQ)	SP + PQ (45 mg/kg)
Malaysia	CQ (1987) SP (1982) *P. vivax* resistance to CQ	CQ	SP
Myanmar	CQ (1969) SP (1986) MQ Q *P. vivax* resistance to CQ (1991)	CQ or SP + PQ (*P. vivax*: CQ)	MQ (15–20 mg/kg) PQ (immunes) Q-7 + PQ (children and non-immunes)
Thailand	CQ (1962) SP (1984) MQ (1990) Q + T (1982–1984)	MQ + PQ (in all areas except as below) MQ + ASU + PQ in multidrug-resistant areas (borders) (*P. vivax*: CQ)	Q-7 + T-7 + PQ (30 mg/kg)
Viet Nam	CQ (1967) SP MQ (southern provinces)	CQ (north) ATM-5 or ASU-5 (other) (*P. vivax*: CQ+PQ-5)	ASU-3 + MQ (25 mg/kg) (north) Q-5 + T-5 (other)
Yemen	CQ	CQ	SP

AQ, amodiaquine; ASU, artesunate; ATM, artemether; CQ, chloroquine; MQ, mefloquine; PQ, primaquine; Q, quinine; RDT, rapid diagnostic testing; SP, sulfadoxine-pyrimethamine; T, tetracycline; ASU-3, artesunate for 3 days, Q-7 quinine for 7 days, etc.

Oceania

Chloroquine resistance is widespread in Papua New Guinea, Solomon Islands and Vanuatu. At an interregional meeting in 1996 that considered drug resistance, the new protocol for *in vivo* testing was adopted. Combinations with and without artemisinins are increasingly being adopted in this region. The current first-line treatment is a combination of sulfadoxine–pyrimethamine and chloroquine (with the variation that children under 5 years of age are treated with amodiaquine) in Papua New Guinea and in Vanuatu, and a decision to adopt this combination is also being considered in Solomon Islands.

Chloroquine-resistant *P. vivax* has been found in Papua New Guinea (40) and the Solomon Islands (unpublished data).

Table 3. Emergence of resistance to antimalarial drugs and treatment policies in selected Oceanic countries

Country	Drug for which reduced susceptibility of parasite reported (year of reporting if known)	Current first-line policy (November 2000)	Current second-line policy
Papua New Guinea	CQ (1976) AQ (1987) Q SP *P. vivax* resistance to CQ (1989–1990)	CQ + SP (adults) AQ + SP (children < 5 years) (*P. vivax*: CQ+PQ-14)	ASU + SP
Solomon Islands	CQ (1980) SP (1995)	(plan to change to CQ + SP) (*P. vivax*: CQ+PQ-7)	CQ + SP (Q)
Vanuatu	CQ (1987) SP (1991)	CQ + SP (*P. vivax*: CQ)	Q

AQ, amodiaquine; ASU, artesunate; CQ, chloroquine; Q, quinine; SP, sulfadoxine-pyrimethamine

Americas

Following a PAHO-sponsored meeting on antimalarial drug resistance in the Amazon region in Manaus in March 1998, several countries have undertaken *in vivo* drug efficacy testing using the revised WHO/PAHO protocol. Thus far, the only changes in drug policy have occurred in Peru (see country examples in section 4.7). The most commonly used replacement therapy for chloroquine was sulfadoxine-pyrimethamine. However, *P. falciparum* resistant to sulfadoxine–pyrimethamine rapidly emerged in Bolivia, Brazil, Colombia, Peru and Venezuela.

P. vivax remains sensitive to chloroquine in the Americas, but cases of vivax malaria that failed to respond to the standard dose of 25 mg of chloroquine base per kg have been reported from Brazil (41), Guatemala and Guyana. Despite occasional reports to the contrary, *P. vivax* resistance to chloroquine has not been confirmed in Peru and Venezuela (42, 43).

Table 4. Emergence of resistance to antimalarial drugs and antimalarial treatment policies in selected countries in the Americas

Country	Drug for which reduced susceptibility of parasite reported (year of reporting if known)	Current first-line policy (November 2000)	Current second-line policy
Brazil	CQ (1961) SP (1972) (*P. vivax* resistance to CQ) MQ (1996)	Q-7 + T-7	MQ 15 mg/kg
Colombia	CQ (1958) SP (1985)	AQ + PQ +SP	SP
Guyana	CQ (1987) SP (1993) (*P. vivax* resistance to CQ)	Q-3 + CD	SP
Peru	CQ (1987) SP (1997)	Q-7 + T-7 (will change very soon to SP + ASU on Pacific Coast and to MQ + ASU in Amazon region)	SP
Venezuela	CQ (1960) SP (1978)	CQ + PQ	Q + D

AQ, amodiaquine; ASU, artesunate; CD, clindamycin; CQ, chloroquine; D, doxycycline; MQ, mefloquine; PQ, primaquine; Q, quinine; SP, sulfadoxine–pyrimethamine; T, tetracycline

Europe

Since the early 1990s, the malaria situation has deteriorated considerably, owing to political and economic instability, massive population movements and large-scale development projects. In recent years, Azerbaijan, Tajikistan and Turkey have suffered explosive and extensive epidemics, while Armenia, Turkmenistan and Georgia have faced small-scale outbreaks. In 1995, a total of 92 048 malaria cases were reported in the Region, mostly vivax malaria. During 1996–2000, the reported total number of malaria cases declined from 91 723 to 32 724. Despite a substantial reduction in the reported incidence of malaria in the Region, the situation is complicated by the occurrence and spread of *P. falciparum* in Tajikistan where 773 cases were reported in 2000. Chloroquine-resistant malaria has not yet been found in countries of the Region where autochthonous cases are reported.

Imported malaria is a growing public health issue, and mortality due to malaria presents a challenging problem to medical professionals in countries of the Region. Since the beginning of 1970s the number of imported cases increased eight-fold: from 1 500 cases in 1972 to almost 13 000 in 1999. The majority (> 80%) of the imported cases of malaria reported in the European Region are acquired in Africa. The largest number of cases has been recorded in France, Germany, Italy and United Kingdom. At present *P. falciparum* accounts for almost 70% of cases. In the period 1989–1999, 680 people are known to have died from malaria in the European Region.

2. COMBINATION THERAPY

2.1 Definitions

Combination therapy with antimalarial drugs (CT) is the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite.

Artemisinin-based combination therapy (ACT) is antimalarial combination therapy with an artemisinin derivative as one component of the combination.

Combination therapies can be either fixed-combination medicinal products, in which the components are co-formulated in the same tablet or capsule, or multiple-drug therapy, in which the components are co-administered in separate tablets or capsules.

Note 1. In accordance with these definitions, the following multiple-drug therapies are NOT considered to be combination therapy:

- use of an antimalarial drug with a non-antimalarial drug that may enhance its action (e.g. chloroquine plus chlorpheniramine),
- use of a blood schizonticidal drug with a tissue schizonticidal or gametocytocidal drug (e.g. chloroquine plus primaquine).

Note 2. Certain medicinal products that strictly speaking fit the criteria of synergistic fixed-dose combinations are operationally considered as single synergistic products in that neither of the individual components in itself would be given alone for antimalarial therapy. Examples include:

- sulfadoxine–pyrimethamine,
- chlorproguanil–dapsone,
- atovaquone–proguanil.

2.2 Rationale for the use of combination therapy

Fixed-combination and multiple-drug therapies are used to exploit the synergistic and additive potential of individual drugs. The aim is to improve efficacy and to retard the development of resistance to the individual components of the combination. This concept has been realized in multiple-drug therapy for leprosy, tuberculosis and cancer and, more recently, in antiretroviral treatments. It has also already been realized to some extent in the field of malaria with the development of such drugs as sulfadoxine-pyrimethamine, atovaquone-proguanil and mefloquine-sulfadoxine-pyrimethamine.

Because of the continued increase of resistance to antimalarial drugs in many regions of the world, with the resultant effect on morbidity and mortality (23), it is essential to ensure rational deployment of the few remaining effective drugs, to maximize their useful therapeutic life while still ensuring that safe, effective and affordable treatment is accessible to those at risk. This require-

ment has resulted in a re-examination of the potential of combinations of existing products and the development of new combination drugs.

The rationale for the impact of CT on drug resistance is based on the assumption that drug resistance essentially depends on mutation. Provided that the constituent drugs administered in the combination have independent modes of action, the probability that a mutant will arise that is simultaneously resistant to both drugs is the product of the respective mutation rates, multiplied by the number of parasite cells exposed to the drugs (8, 10, 44). For example, if two drugs are used, and for each one a single mutational event confers complete resistance and such events occur with a frequency of $1:10^{10}$ nuclear divisions, then the probability of a mutation resistant to both drugs is $1:10^{20}$. The number of asexual parasites (parasite biomass) during an acute malaria infection is usually between 10^9 and 10^{14} (44).

2.3 Artemisinin-based combination therapy

The particular features of ACT relate to the unique mode of action of the artemisinin component, which includes the following:

- rapid and substantial reduction of the parasite biomass,
- rapid parasite clearance,
- rapid resolution of clinical symptoms,
- effective action against multidrug-resistant *P. falciparum*,
- reduction of gametocyte carriage, which potentially reduces transmission of resistant alleles.

There are also few reported adverse clinical effects (45), although preclinical toxicology data on many artemisinin derivatives are limited.

Because of the short half-life of artemisinin derivatives, their use as monotherapy requires daily doses over a period of 7 days. Combination of one of these drugs with a longer half-life partner antimalarial drug allows a reduction in the duration of antimalarial treatment while at the same time enhancing efficacy and reducing the likelihood of resistance development. The major immediate effect of the artemisinin component is to reduce the parasite biomass. The residual biomass is exposed to maximum concentrations of the partner drug, well above its minimum inhibitory concentration, resulting in a lesser likelihood of resistant mutations breaking through.

In most of the artemisinin-based combinations currently in use or being evaluated, e.g. artesunate–mefloquine, the partner drug is eliminated slowly. The partner drug is therefore unprotected once the artemisinin has been eliminated from the body and operates a selective pressure on new infections. The implications of this "pharmacokinetic mismatch" are not fully understood at present, particularly in areas of high transmission in Africa. The safest approach is to use a drug partner that has a residual half-life as short as possible, while still enabling parasite clearance with a 3-day treatment. However, this is difficult to achieve given the limited range of antimalarial drugs available.

There is a growing interest in using antimalarial combinations containing an artemisinin derivative as first-line treatment. The aim is to provide efficacious and safe antimalarial drug treatment while probably delaying the onset and spread of resistance to both drugs in the combination. This interest results from experience with the combination of artesunate and

mefloquine on the Thai-Myanmar border (12, 13, 46–49). Following the introduction of the combination there have been four principal clinical and epidemiological effects:

- the efficacy of the combination has exceeded 95% at a time when high-dose mefloquine was showing a failure rate of approximately 25%,
- this high efficacy has been sustained over the past 7 years,
- the transmission of *P. falciparum* has been reduced (with reduced gametocyte carriage from the artesunate),
- the *in vitro* sensitivity of mefloquine has increased, suggesting that the combination has reversed the previous decline in mefloquine sensitivity.

These studies have been conducted in areas where there is a high level of medical service provision and malaria transmission is low. It is not yet known whether similar results can be achieved in Africa and other high-transmission regions. Moreover, evidence of the effectiveness of ACT in delaying the development of resistance is not yet available in Africa. Clinical trials using combinations of artesunate with amodiaquine, chloroquine, sulfadoxine–pyrimethamine or mefloquine are currently in progress to assess the efficacy and safety of ACT for treating uncomplicated falciparum malaria in Africa, South America and Asia.

Factors for and against the introduction of ACT are summarized in Table 5. ACT should be considered in two different settings. In places where the combination is presently more efficacious than available monotherapies, such as parts of South-East Asia, it has a clear role. In areas where monotherapy is still efficacious but where this may change if the drug concerned is not protected from resistance, the justification for introducing ACT is less clear at the operational level. Although the general theory behind the promotion of ACT is widely accepted, doubts remain about the quantitative impact it will have in real-life situations. Ministries of health are therefore reluctant to commit to a high-cost ACT strategy where the merits of the different options available remain unclear and significant operational barriers still need to be overcome.

Time is a major constraint to this process: a change is needed now in several countries where chloroquine has poor efficacy. There are profound concerns that a change from chloroquine to sulfadoxine–pyrimethamine monotherapy might affect the future utility of some ACTs, in particular sulfadoxine–pyrimethamine plus artesunate, and chlorproguanil–dapsone (LapDap) plus artesunate. Urgent information is needed on the effectiveness of chloroquine or amodiaquine combined with sulfadoxine–pyrimethamine as a possible interim measure while attempts are made to assess and improve on the cost-effectiveness of ACTs in the African context.

Table 5. Factors for and against the introduction of artemisinin-based combination therapy

FOR	AGAINST
• The need to replace inadequate drug regimens that are leading to increased malaria-related mortality and morbidity	• Higher cost
• Potential avoidance of the loss of available effective and affordable antimalarial drugs, especially in Africa	• Problems of adherence to non-fixed combinations and their rational use, particularly in the home
• Excellent efficacy (both clinical and parasitological clearance) of artemisinin derivatives, with no resistance reported from South-East Asia despite extensive use	• Lack of extensive clinical experience with most of the combinations currently under investigation
• Potential reduction in transmission (especially of resistant mutants) due to the gametocytocidal effect of artemisinin derivatives	• Lack of evidence so far in Africa of its effectiveness in delaying the development of resistance
	• Importance of not misusing artemisinin derivatives in view of their role in the treatment of severe malaria

2.4 Implementation of combination therapy—operational issues

It would appear logical that, if CT is to delay the development of resistance, existing monotherapy with either of its components should cease, although this has not been rigorously proven. In order to minimize monotherapy with the components of a particular CT, therefore, it is necessary to guarantee consistent access to the CT and restrict access to related drugs throughout the health sector, both private (formal and informal) and public. Fixed-combination products are preferred to multiple-drug therapy as this will improve the ease of use and compliance, while minimizing the potential use of components of the combination as monotherapy. Price to the user and to the health system must be competitive with alternatives and affordable to the poorest, otherwise the public health value of CT may be compromised.

Other areas where improvement is critical for successful implementation of CT relate to generic issues of policy implementation. They include training and motivation of health workers, public confidence in and use of health facilities, reliable drug supplies, a regulated private sector and good quality control to prevent infiltration of counterfeit drugs.

With the increased use of new combinations, safety assessments, monitoring of potential drug interactions and strategies for the treatment and protection of pregnant women are urgently required. Similar strategies for application in complex emergency situations, with a particular emphasis on compliance, are also essential. With support from external agencies, implementation of CT in the short term, in defined areas, may be feasible. However, greater efforts and resources are needed in isolated areas with poor services to ensure the sustainability of policies and programmes.

It is anticipated that, in some settings, CT could be introduced to protect the life span of a still effective antimalarial monotherapy. In these cases, CT will be of long-term benefit to the community rather than of immediate benefit to the patient. The substantially higher cost of CTs is probably the major obstacle to the implementation of this strategy, especially in sub-Saharan Africa. As a public health measure subsidies could be justified, but assurance is needed that financial mechanisms will be sustainable.

3. Chemoprophylaxis and treatment of malaria in special groups

The principles of the use of antimalarial drugs for protection against malaria and the treatment of uncomplicated malaria were reviewed in 1995 (16). This section considers the particular requirements for chemoprophylaxis in pregnant women and for chemoprophylaxis and stand-by treatment in travellers. It also comments on the management of severe malaria, the treatment of vivax malaria and the need for antimalarial formulations for paediatric use.

3.1 Guiding principles of chemoprophylaxis and intermittent treatment of malaria during pregnancy

Malaria infection in pregnancy poses a substantial risk to the mother, the fetus and the newborn infant. Pregnant women are less capable of coping with and clearing malaria infections. In areas of low transmission of *P. falciparum*, where levels of acquired immunity are low, women are susceptible to attacks of severe malaria, which may result in stillbirths or spontaneous

abortions, or the death of the mother. In areas of high *P. falciparum* transmission, levels of acquired immunity tend to be high and women may have asymptomatic infections, which may result in maternal anaemia and placental parasitaemia. Both of these conditions can lead to low birth weight, an important contributor to neonatal mortality.

In programmes for the prevention or treatment of malaria in pregnant women, two major issues are the safety and effectiveness of the antimalarial drug regimen. The programmatic effectiveness of a given drug is determined by the efficacy of that drug against the parasite and by the drug's characteristics, including affordability, availability, acceptability to the target population, and deliverability in terms of dosing requirements and incorporation into existing antenatal care delivery systems.

Weekly chloroquine chemoprophylaxis and preventive intermittent treatment with sulfadoxine–pyrimethamine during pregnancy have both been shown to reduce the rate of placental parasitaemia and low birth weight (50). Many national antimalarial treatment policies include a recommendation for chloroquine chemoprophylaxis. It is rarely implemented, however, because of problems with compliance, fears about adverse effects of the drug during pregnancy, and the concern of health workers that use of drugs for this purpose may deplete stocks needed for the treatment of acute infections.

An increasing number of countries, e.g. Malawi, are implementing intermittent treatment with 2- or 3-dose treatment regimens of sulfadoxine–pyrimethamine: once in the second and once or twice in the third trimester (51–53) to prevent malaria in pregnancy. In HIV-positive women, the 3-dose treatment is significantly more efficacious than the 2-dose regimen (51). It has been suggested that sulfadoxine–pyrimethamine should ideally be reserved for preventive intermittent treatment in pregnancy (R. Steketee, personal communication, 2000). In many endemic areas where sulfadoxine–pyrimethamine is one of the few replacement therapies for chloroquine, this may not be a viable option.

3.2 Guiding principles of chemoprophylaxis and stand-by treatment in travellers

The spread and intensification of drug resistance worldwide has greatly complicated recommendations for the prevention of malaria in travellers. Travel to malarious areas is on the increase, while many countries are experiencing a resurgence of malaria. As a short-term measure, chemoprophylaxis is recommended for international and national travellers from non-endemic areas, and for soldiers, police and labour forces serving or working in highly endemic areas. Detailed recommendations for the protection of travellers against malaria are updated and published annually by *WHO in International travel and health: vaccination requirements and health advice* (54).

All travellers to malarious areas should be clearly informed of: the risk of malaria; how they can best protect themselves against mosquito bites; the use of chemoprophylaxis wherever appropriate; and the need to seek early diagnosis and treatment if symptoms suggestive of malaria occur. Malaria must always be suspected if fever, with or without other symptoms, develops at any time between one week after the first possible exposure to malaria and two months (55), or even longer in exceptional cases, after the last possible exposure. Nearly all travellers who acquire a *P. falciparum* infection will have developed symptoms within 3 months of exposure (56). Medical attention should be sought and a blood sample examined for malaria parasites. If no parasites are found but symptoms persist, a series of blood samples should be taken and examined at

appropriate intervals. Relapses of vivax and ovale malaria are not prevented by chemoprophylaxis with currently used prophylactic regimens.

Malaria chemoprophylaxis should be selected on the basis of an individual risk assessment of the traveller, an assessment of the safety and efficacy of potential chemoprophylactic regimens, and drug resistance and the extent of malaria transmission in the region to be visited. Weekly prophylactic antimalarial regimens should normally be started one week before travel. Daily drugs such as proguanil and doxycycline should be started the day before travel. Drugs should then be taken with unfailing regularity for the duration stay in the area of malaria risk, and continued for 4 weeks after leaving the endemic area. The exception is atovaquone/proguanil, which can be stopped one week after leaving the area with malaria risk. Mefloquine prophylaxis should preferably be started 2-3 weeks before departure, so that adequate blood levels are attained, and adverse reactions can be detected before travel, allowing consideration of alternative drug regimens. Antimalarial drugs should be taken with food and swallowed with plenty of water.

In general, travel areas are classified as:

- ***Areas with P. vivax transmission only.***
- ***Chloroquine-sensitive***—Malarious areas where chloroquine resistance has not been documented or is not widely present; these include Haiti, the Dominican Republic, Central America north-west of the Panama Canal and parts of the Middle East.
- ***Chloroquine-resistant***—Most of Africa, South America, Oceania and Asia.
- ***Chloroquine- and mefloquine-resistant***—Resistance to both chloroquine and mefloquine is not a significant problem except in rural forested regions along the borders between Cambodia, Myanmar and Thailand, which are infrequently visited by tourists; mefloquine resistance in varying degrees has been reported from Brazil, Cambodia, China (*in vitro*), French Guyana, Myanmar, Thailand and Viet Nam.

Data on the incidence of malaria and the effectiveness and tolerance of currently recommended chemoprophylaxis and self-treatment regimens for long-term travellers are limited. Chloroquine and mefloquine has been shown to be safe for at least 3 years. In chloroquine-resistant regions, mefloquine is more efficacious than the chloroquine plus proguanil combination (57, 58). In one study, chemoprophylaxis with atovaquone–proguanil for 20 weeks and with primaquine for 50 weeks had no significant adverse effects (59, 60).

Malaria prevention in young travellers

Children are at special risk of malaria since they may rapidly become seriously ill. Persuading young children to take antimalarial medications may be difficult because of the lack of paediatric formulations and the bitter taste of many drugs. Furthermore, some chemoprophylactic drugs are contraindicated in children. Chloroquine remains the drug of choice in areas where malaria remains sensitive to this drug, while mefloquine is the preferred agent in chloroquine-resistant areas. Although the manufacturer recommends that mefloquine should not be given to children who weigh less than 5 kg, it should be considered for chemoprophylaxis of all children at high risk of acquiring chloroquine-resistant *P. falciparum* malaria. Atovaquone–proguanil may be a safe and effective chemoprophylactic alternative to doxycyline for children under 8 years of age who weigh more than 11 kg and are travelling to mefloquine-resistant areas.

Malaria prevention for travellers during pregnancy

In non-immune pregnant travellers, malaria increases the risk of maternal and neonatal death, miscarriage and stillbirth. When travelling to malarious areas, pregnant women should take special care to avoid mosquito bites.

Chloroquine is known to be safe in pregnancy, but its usefulness is limited to a few areas with chloroquine-sensitive strains of *P. falciparum*. Available data indicate that mefloquine is safe as a chemoprophylactic agent after the first trimester. Becoming pregnant while taking mefloquine chemoprophylaxis is not an indication for termination of the pregnancy. The combination of chloroquine plus proguanil is safe in pregnancy and provides more protection than chloroquine alone in areas with known chloroquine-resistant strains, but is significantly less efficacious than mefloquine (61, 62). Doxycycline and primaquine are contraindicated during pregnancy. Data on the safety of atovaquone–proguanil during pregnancy are insufficient, although studies with this combination are currently under way.

Stand-by emergency treatment for travellers

Most travellers to urban or major tourist areas will be able to obtain prompt and reliable medical attention when malaria is suspected. However, a minority may be travelling to such isolated locations that they will have no access to competent medical attention within 24 h after the onset of symptoms, a week or more after first possible exposure. In such cases, stand-by emergency treatment should be prescribed to the traveller for self-administration should symptoms occur (63–66). Precise instructions should be given on the recognition of malaria symptoms and the need to take the full treatment dose of the drug, and information should be provided on possible adverse reactions. Travellers must also be made aware that they should seek attention as soon as possible after symptoms appear and they begin their stand-by treatment, and that stand-by treatment is not a substitute for diagnosis and treatment by qualified medical personnel.

Because of the potential for additive toxicity and reduced efficacy, individuals who are on chemoprophylaxis should never attempt stand-by-treatment with the same drug. Following completion of the treatment, individuals should resume effective malaria chemoprophylaxis. As a general guide, chemoprophylaxis should be restarted one week after the first treatment dose. When the stand-by-treatment is quinine, however, mefloquine chemoprophylaxis should be restarted one week after the last dose (54).

Chloroquine, sulfadoxine–pyrimethamine, mefloquine, quinine plus tetracycline, atovaquone–proguanil and artemether–lumefantrine can be prescribed as stand-by treatments, depending on the drug-resistance status of the parasites in the areas to be visited. Halofantrine is not recommended owing to the fact that it can result in ventricular dysrhythmias and prolongation of QTc intervals in susceptible individuals. While the antimalarial drugs described above are all used for stand-by treatment, artemether plus lumefantrine is the only therapy registered by a national drug regulatory authority for this purpose (67). Efficacy, safety and ease of administration should be considered for the selection of stand-by treatment, but there is some concern about the use of drugs for this purpose in travellers who may have access to medical facilities.

3.3 Management of severe malaria

Treatment with antimalarial drugs has a major role to play in preventing severe malaria and death. It reduces fever promptly and effectively to interrupt the progression of infection or mild illness to severe disease, and reduces fatality rates in severe malaria. Since the great majority of patients with fever or other symptoms suggestive of malaria receive their initial treatment at home, improving home management of fever is a critical component of this process. Patients and their families need up-to-date and practical guidance on when and how to use antimalarial drugs at home, on how to recognize when a patient is not responding to therapy in order to seek medical attention, and on the importance of correctly following, at home, the recommendations and treatments that are given in health centres and hospitals. This guidance should be complemented with more user-friendly treatment regimens, improved formulations, especially for the treatment of children, and pre-packaging of antimalarial tablets.

At the health post or health centre level, availability of effective drugs is crucial. Health workers need clear guidelines on how antimalarial drugs should be used and how to deal with potential adverse reactions. In addition, there should be facilities to administer fluids, glucose, antibiotics, and anticonvulsants to severely ill patients. In suspected cases of severe malaria, rectal formulations of the artemisinin drugs and other preparations can be used as an emergency pre-referral treatment when parenteral antimalarial therapy is not available, and have the potential to reduce early mortality. In hospitals, prompt confirmation of diagnosis, rapid assessment of the severity of disease and the administration of prompt specific and supportive treatment, including safe blood for transfusion, are all critical. These issues are covered thoroughly elsewhere (15).

3.4 Vivax malaria

P. vivax is the predominant malaria species in most of Asia (including the Indian subcontinent), Oceania, North Africa, and Central and South America and is estimated to account for about 55% of the total malaria incidence outside subtropical Africa. In recent years, there has been a major resurgence of vivax malaria in eastern Europe and central Asia, areas which had been free of malaria for several decades. The major threat to the control of *P. vivax* today is the emergence and spread of chloroquine-resistant strains in Guyana, India, Indonesia (Irian Jaya), Myanmar and Papua New Guinea (68).

The existence of strains of *P. vivax* that differ in their relapse patterns and their innate sensitivity to primaquine influences the choice of regimen for radical cure. For strains of *P. vivax* from Papua New Guinea, Solomon Islands and Vanuatu, and parts of Indonesia, a total dose of primaquine base of 7 mg/kg (equivalent to 420 mg in an adult) given as 30 mg of primaquine base daily for 14 days, is required to achieve 100% cure rates. Strains from China, South-East Asia, central Asia, the Middle East, northern Africa, and Central and South America can be cured with half this dose. There is limited evidence that strains from the Indian subcontinent may respond to a 5-day course of 15 mg of primaquine base (69, 70).

3.5 Formulations for paediatric use

In Africa, particularly in areas of high transmission, children under 5 years of age are the most affected by malaria, leading to a high case fatality rate in this age group. In spite of the

importance of the disease in children and the fact that they are the major targets for antimalarial drugs, there are problems with existing paediatric formulations and regimens:

- Many tablet formulations are not scored, making it difficult to break the tablets into halves and quarters as required by current treatment regimens.
- Confusion arises from the availability on the market of some drugs at more than one strength (e.g. chloroquine as tablets of 100 mg and 150 mg base).
- Different spoon sizes lead to inconsistencies in the dosing of syrups.
- Syrups are often dispensed in volumes of 100–120 ml, tempting mothers to continue administering until finished, or to save the medication for administration to other children.
- Confusion arises because there are four different age groups for treatment with chloroquine in children under 5 years.

These and similar problems influence patient adherence and result in both underdosing and overdosing. Increasing attention to this area through operational research is beginning to suggest some solutions. Appropriate packaging and labelling improves compliance, enhances acceptability (71–74) and greatly reduces the risk of overdosing (74–77). Adherence to prepackaged tablets is much better than to syrup, and the cost of prepackaged treatments is much lower (76). Training health facility workers and equipping them with packaged treatments have been shown to reduce case fatality rates (78). Prepackaging of drugs for specific age and weight ranges (76) can improve home management of malaria. It now remains to translate these research findings into practice.

4. Antimalarial treatment policies

4.1 Definition

An antimalarial treatment policy is a set of recommendations and regulations concerning the availability and rational use of antimalarial drugs in a country (79). It should be part of the national essential drug policy and the national malaria control policy and in line with the overall national health policy.

4.2 Purpose

The primary purpose of an antimalarial treatment policy is to select and make accessible to the populations at risk of malaria safe, effective, good quality and affordable antimalarial drugs so that malaria disease can be promptly, effectively and safely treated. The definition of effective treatment may vary in different epidemiological situations as follows:

In areas of intense transmission: clinical cure, i.e. clinical remission including the prevention of clinical recrudescence (no appearance of signs and symptoms in the 14 days following treatment).

In areas of low transmission: parasitological or radical cure, i.e. elimination of all parasites from the body.

In areas of intense transmission and high population immunity, infected adults are often asymptomatic and clinical cure can be achieved without parasitological cure. In areas of low transmission and low population immunity, asymptomatic infections are rare and clinical cure can rarely be achieved without parasitological cure.

A second purpose is to prevent or delay the development of antimalarial drug resistance by correct diagnosis and rational drug use.

In certain countries and situations, a third purpose may be radical cure of all malarial infections with the objective of reducing transmission through the use of a gametocytocidal drug. Such an objective would be unrealistic in areas of intense transmission and high population immunity where asymptomatic infections are common, but may be realistic in areas of low transmission, if high treatment coverage can be achieved and/or vector control is carried out as a complementary measure.

An effective treatment policy should aim to:

- reduce morbidity,
- halt the progression of uncomplicated disease into severe and potentially fatal disease, and thereby reduce malaria mortality,
- reduce the impact of placental malaria infection and maternal malaria-associated anaemia through chemoprophylaxis or preventive intermittent therapy,
- minimize the development of antimalarial drug resistance.

4.3 Development

The categories for the treatment of malaria include drugs for first-line treatment (the treatment given to probable malaria, or confirmed malaria), second- and third-line treatment (given to treatment failures), severe malaria, pregnant women, presumptive treatment, self-treatment/over-the-counter treatment and mass treatment (recommended in epidemics). The antimalarial treatment policy must provide indications for all these treatment categories. However, the choice of first line treatment has the greatest economic implications and the greatest public health implications.

The essential components for developing and updating national treatment guidelines for antimalarial drugs include:

- clear analysis of the technical, social and economic issues related to malaria control, antimalarial drug resistance, potential interventions and the consequences of action or inaction,
- analysis of the decision-making environment,
- consensus-building among relevant stakeholders (policy-makers, researchers, control staff, donors, private providers, industry and user representatives),
- a supervisory body to oversee the development, implementation and revision of the policy,
- a regulatory body to ensure adherence to policy components.

A critical starting point for developing or updating antimalarial treatment policy is an assessment of the status of antimalarial drug efficacy. Standardized approaches for assessing antimalarial drug efficacy should be used to allow for trends to be monitored and comparisons made.

4.4 Factors influencing antimalarial treatment policies

Antimalarial drug resistance and policy-making are dynamic areas, and the situations in each country may vary depending on disease epidemiology, transmission, drug resistance patterns and political-economic contexts. In general, the policy process requires information from a variety of sources:

- analysis of the epidemiological situation, including type of parasite species,
- levels of resistance to currently used antimalarial drugs,
- evaluation of the properties of available alternative drugs,
- analysis of treatment-seeking behaviour—provider and consumer behaviours, which may reflect whether the existing policies are rational and thus also influence how they will be implemented,
- cost-effectiveness analysis of alternative therapies; the costs of implementing antimalarial treatment policies include the administrative and logistical costs, while costs for changing policies should include the actual cost, dissemination of revised guidelines and training,
- analysis of health system capacity to implement the revised policy, including the necessary regulatory and legislative framework.

Several factors may influence the selection of antimalarial therapies (see below); they are considered further below. Additional guidance on the selection of drugs for antimalarial treatment policies is given in Annex 2.

Properties of antimalarial drugs that may influence their selection

- Efficacy and half-life
- Acceptability and adherence to treatment (including different formulations)
- Effectiveness
- Quality
- Adverse effects
- Drug interactions and contraindications
- Use in special groups, e.g. pregnant women and infants
- Capacity of health system to implement policy
- Cost, cost-effectiveness, and affordability of various regimens
- Reported resistance and/or cross-resistance
- Useful therapeutic life

Efficacy

Drug efficacy is determined by the drug sensitivity of the Plasmodium species concerned, pharmacokinetics and the development of resistance as a function of time (influenced by the drug's half-life). In developing or revising an antimalarial treatment policy, the efficacy of alternative regimens should also be taken into account.

Acceptability and adherence to treatment

Acceptability and adherence to treatment by patients are major components in the success of any public health system and are influenced by both behavioural and economic factors. They are determined by:

- duration of treatment,
- number of daily doses,
- speed of clinical response, in particular the antipyretic effect,
- minor adverse effects,
- market-price relative to household economy or affordability,
- presentation, packaging, health education (consistent IEC messages),
- taste and/or colour, and size of tablet (or volume per dose for syrups and suspensions),
- reputation of the drug.

Simple technology, like blister packaging of antimalarial drugs, may offer some solutions to the problem of incorrect use (78).

Effectiveness

Effectiveness is determined by efficacy and adherence to the treatment (see above).

Quality

Drug quality should be considered at all stages of the drug management cycle, including selection (80). Poor quality drugs decrease efficacy, affect the reputation of the drug and undermine the treatment policy. Quality assurance is an important component of pre-registration and post-marketing surveillance.

The WHO Model List of Essential Drugs

Essential drugs are those drugs that satisfy the health care needs of the majority of the population; they should therefore be available at all times, at a price they and the community can afford, in adequate amounts and in appropriate dosage forms (81). In most countries, the selection of essential drugs is a two-step process. Firstly, market approval of a pharmaceutical product is usually granted on the basis of efficacy, safety and quality. Secondly, an evaluation is made on the basis of a comparison between various drug products for a given indication and their "value for money."

The WHO Model List of Essential Drugs serves as a model for the second step in this selection process and for national and institutional essential drug lists, although inclusion of a new drug on the WHO Model List is not a regulatory decision and is not binding on national governments. The Model List currently includes 306 active compounds and is updated every two years. The list contains a section on antimalarial drugs (81). Selection of drugs for inclusion on this list is based on the following criteria:

- sound and adequate data on efficacy and safety from clinical studies,
- availability in a form in which quality, including adequate bioavailability, can be assured,
- stability under the anticipated conditions of storage and use,
- cost-effectiveness of the treatment.

By the end of 1999, 146 Member States had official national lists of essential drugs, which serve as guides for the supply of drugs, including antimalarial drugs where appropriate, in the public sector in their respective countries.

Registration and regulation

Antimalarial drugs, like other medicines, are regulated by national drug regulatory authorities within ministries of health. The regulation and control of pharmaceutical products, including drug registration, quality assurance, and inspection of the distribution system, is in accordance with national pharmaceutical legislation and national drug policy. Supplementary legislation including regulations, norms, standards, specifications, guidelines and procedures is also taken into account. In developing countries, national drug regulatory authorities are at various stages of evolution. Their core functions include drug registration, overall quality assurance of pharmaceutical products, surveillance of drug distribution channels, and control of information and promotion.

For registration of pharmaceutical products, the most frequently applied criteria are efficacy, safety and quality. National drug regulatory authorities approach overall quality assurance by combining quality assurance of pharmaceutical manufacturers (with regard to good manufacturing practices, GMP) with an effort to ensure that the pharmaceutical products available on the market meet the prescribed quality specifications.

Assuring the quality of pharmaceutical products on the market is an expensive process in which a careful selection of products to be sampled and tested has to be made. Some countries have developed national regulatory laboratories specifically for this purpose, while others have chosen to contract with external laboratories for the necessary analyses. To ensure that registered products continue to comply with the regulatory requirements after they have been registered, a complement of well-trained pharmaceutical inspectors is needed for surveillance of pharmaceutical manufacturing plants, ensuring adherence with GMP as well as ensuring that the pharmaceutical products available on the market through the various drug distribution channels meet the prescribed quality specifications.

The distribution of a product, within the marketing authorization granted, is linked to scheduling of drugs within the country, therapeutic category and specific indication(s) for the product, presentation of the product (dosage form), accompanying literature/information, ease of use of the product, and the expected level of training required to ensure safe use of the product.

Cross-resistance

Chemically related antimalarial drugs, e.g. chloroquine and amodiaquine, may give rise to similar patterns of resistance. However, the extent to which the degree of development of resistance to amodiaquine is due to resistance to chloroquine is unclear. Similarly, the extent to which the widespread use of sulfadoxine–pyrimethamine for malaria treatment or sulfamethoxazole-trimethoprim (cotrimoxazole) for bacterial infections may compromise the utility of other sulfa drugs, such as chlorproguanil–dapsone, is not known.

Adverse effects

Mild adverse effects, such as itching and gastrointestinal effects may influence adherence to treatment and choice of drug. The risk of severe adverse effects, such as neuropsychiatric effects or agranulocytosis, must be considered when deciding policy.

Drug interactions

Some drugs given concurrently or sequentially produce undesired effects. For example, folate supplementation can inhibit the action of sulfadoxine–pyrimethamine, increasing the likelihood of treatment failure. Quinine, mefloquine and halofantrine given close together are potentially cardiotoxic. Complementarity and potential synergistic effects must also be taken into consideration.

Use in special groups

Pregnancy is a contraindication for many antimalarial drugs (82). The risk to the mother and fetus must be carefully weighed against the risk of malaria. High-risk groups, such as non-immune refugee populations, may need a first-line drug that is different to that recommended in the national antimalarial treatment policy in hyper- and holoendemic areas. The full effects of HIV on the efficacy and adverse effects of antimalarial drugs are not yet known. Some preliminary data indicate a higher risk of adverse effects with sulfadoxine–pyrimethamine in HIV-positive patients with Plasmodium infections than in HIV-negative patients (83). The safety and effectiveness of some antimalarial drugs has not been established in infants, e.g. atovaquone–proguanil, artemether-lumefantrine, halofantrine and mefloquine. The tetracycline group of drugs is contraindicated in children under 8 years of age because of its effect bone growth and dental enamel. In additon, primaquine and sulfadoxine–pyrimethamine have age-specific contraindications in children.

Health system capacity to implement the policy

If an antimalarial treatment policy is to be successful, access to good quality essential drugs and health care is vital. Various national strategies exist to finance, distribute and dispense safe, effective and good quality drugs to those who need them. The health system requires political support and financial, managerial, technical and human resources to manage the drug supply and implement the policy effectively. These should be assessed in the context of health sector reform and decentralization. It is also essential to recognize that in many countries health care is sought outside formal health facilities. The role of the government in ensuring quality of service through the informal private sector should also be assessed.

Cost, cost-effectiveness and affordability analysis

To make decisions on whether or not to change the first-line therapy for malaria and what the change should be, policy-makers need information on the health outcomes, cost implications and cost-effectiveness of different regimens. Knowledge of the current and projected annual quantity of first-line and second-line treatments is also critical to the decision-making process. There is a wide spectrum of costs and health outcomes and the evolution of these costs and effects over time must be considered.

Information on the prices of many generic drugs bought in bulk is available from the International Drug Price Indicator Guides produced by Management Sciences for Health, in collaboration with WHO. The average cost per treatment depends on the choice of drug and on the formulations used. The average cost per adult treatment with a range of antimalarial drugs and formulations is shown in Table 6.

A cost-effectiveness analysis involves consideration of the incremental costs and health effects of implementing an intervention, compared with either the status quo, or a different intervention. For example, in considering the introduction of sulfadoxine–pyrimethamine as a new first-line

drug, a comparison could be made with the costs and effects of continuing to use chloroquine or any other treatment. Alternatively the cost of changing immediately to sulfadoxine–pyrimethamine could be compared with changing after a delay of 3 or 5 years.

The analysis must also take into account other costs involved in implementation, such as the need for consultation, consensus-building and policy formulation, revision and production of treatment guidelines, training of public and private sector health workers, and communication and publicity. The managerial capacity requirements and financial costs of these activities are significant. Country-specific costs will depend on the implementation activities selected. A retrospective analysis showed that the change from chloroquine to sulfadoxine–pyrimethamine as the first-line treatment in Malawi cost about US$ 612 000 or US$ 0.06 per capita. An estimated budget for the planned change in the United Republic of Tanzania indicated a total cost of US$ 424 000 over an 18-month period, equivalent to US$ 0.01 per capita, or 1% of the total annual Ministry of Health budget for 1998–1999 (84, 85).

In addition to the direct benefits of reduced malaria mortality and morbidity, changing the first-line therapy to a more efficacious drug may bring other measurable improvements as a result of the reduction in the caseload of malarial illness. Firstly the quality of care may be improved, owing to reductions in the frequency of drug and laboratory supply stockouts, less pressure on staff and reduced patient waiting time. At the same time, more patients with other conditions may get access to care. Secondly, by avoiding return visits to formal health facilities and additional visits to other treatment sources, such as pharmacies, shops and traditional healers, patients will benefit from a reduction in direct expenditure and the time diverted from productive activities as well as the burden of anaemia and other consequences of disease progression. In addition, the use of transmission-blocking drugs such as artemisinin and its derivatives may reduce the incidence of new cases (9), especially in low-moderate transmission areas.

Cost-effectiveness models are simplifications of reality, and the relevance of assumptions and parameter estimates to a particular setting must be carefully considered. Such analysis cannot provide definitive conclusions on the relative cost-effectiveness of different strategies, or resistance thresholds above which a change in first-line drug should definitely be made. However, it does provide a framework for consolidating information on epidemiological, cost and behavioural factors, and indicates ranges for the likely economic and health impacts of different strategies.

The main properties of existing antimalarial drugs and those under development are presented in Annex 3. A summary of the characteristics of selected commonly used antimalarial drugs is provided in Table 6.

4.5 Health-seeking behaviour

The analysis of health-seeking behaviour is essential in developing and implementing a rational drug policy. For example, information on the factors that influence the recognition and interpretation of childhood fevers by consumers and providers, and subsequent choice of therapy will assist in the formulation of guidelines to improve adherence to treatment and treatment effectiveness. These in turn may influence the development of drug resistance. If a treatment does not produce the expected result, patients and care-givers may re-diagnose the cause of the fever (86). It is widely accepted that human behaviours leading to inadequate dosing, incomplete courses of therapy and indiscriminate and inappropriate drug use have contributed to the emergence and spread of resistant parasites (87). It must also be recognized that new treatment policies that replace long-familiar drugs and alter well-established patterns of care seeking and health care practice may fall short of the expectations of patients and care-givers.

As most malaria treatment occurs in the home, changing the first-line drug in the public sector alone may not have a substantial impact. The role of the private sector is crucial in ensuring that drug distribution systems reflect public health policy and that the recommended treatment is available through all types of health care outlets used by the population. Household and community-level antimalarial drug use represents an important entry point for malaria control programmes in most African nations (88). In Africa, shops are the main source of antimalarial drugs (88–91). However, the course of treatment sold is often suboptimal (92–94).

Table 6. Summary of the characteristics of common antimalarial drugs that should be considered in drug selection, including cost of an adult treatment course.

	Evidence of resistance	Reported resistance	Adverse effects	Treatment duration (days)	Adherence to treatment	COST (US$)
CQ	+	YES[a]	+	3	++	0.070
SP	+	YES[b]	++	1	+++	0.082
Q	+	YES[c]	++	7	+	1.350
AQ	+	YES[d]	+++	3	++	0.150
ASU	–	none yet	+ / ++	7	+	2.160
MQ (25 mg/kg)	+	YES[e]	++	2	++	3.220
HAL	+	none yet	+++	2	++	4.750
Q + D	– (?)	none yet	++	7	+	1.470
Q + T	– (?)	none yet	++	7	+	1.650
Q + SP	– (?)	none yet	++	3	++	0.660
CQ + SP	+ (?)	YES	++	3	++	0.154
MQ + ASU	–	none yet	++	3	++	5.380
AT – PR	– (?)	none yet	+ (?)	3	++	42
ART – LUM	–	none yet	+ (?)	3	++	2.5[g]

AQ, amodiaquine; ART–LUM, artemether–lumefantrine; ASU, artesunate; AT–PR, atovaquone–proguanil; CQ, chloroquine; CT, combination therapy; D, doxycycline; HAL, halofantrine; MQ, mefloquine; Q, quinine; SP, sulfadoxine–pyrimethamine; T, tetracycline

[a] South-East Asia, East and South Africa
[b] South-East Asia, East Africa, Amazon Basin, Bangladesh, Oceania
[c] Some parts of Asia
[d] Many areas in Asia and Africa
[e] Thai-Cambodian and Thai-Myanmar borders (sporadic reports in other areas)
[f] Selection depends on the level of resistance to both components
[g] Price available through WHO.

Operational research is needed to determine ways of improving prescribing practices, involving drug vendors and other informal sector providers, and achieving the successful replacement of one drug with another. This should be supported by careful documentation of programme experiences as new policies are implemented. Studies have shown that in-service training can improve the ability of health workers to diagnose and treat clinical malaria (95) and that treatment charts may result in more appropriate dosing of antimalarial medication (96).

4.6 Criteria for changing treatment policy

The primary indicator for changing antimalarial treatment policy is a high level of treatment failure with the currently used antimalarial drug. Conditions that signal a need for a re-evaluation of the policy are:

- evidence from therapeutic efficacy studies,
- evidence of increased malaria-associated mortality and morbidity,
- consumer and provider dissatisfaction with the current policy,
- evidence on new drugs, strategies and approaches.

Evidence from therapeutic efficacy tests

The current WHO standard protocol for the assessment of therapeutic efficacy of antimalarial drugs (29) focuses on the clinical efficacy of the drug, rather than the previously recommended parasitological responses. Treatment failure rate remains the cardinal parameter. It is the most easily measured indicator of efficacy, and its consequences are more or less understood and can be translated into economic terms. Incomplete parasitological cure may lead to anaemia or return of clinical illness which can progress to severe disease. An optimal antimalarial drug should therefore succeed in achieving clinical cure, and in clearing parasites and maintaining the parasite-free period for as long as possible.

When to change

There are no well-defined criteria for determining the level of clinical or parasitological failures with the current antimalarial therapy at which a first-line drug should be replaced. The decision to change is based on a range of factors including the prevalence and geographical distribution of documented treatment failures, the impact of treatment failures on mortality and severe morbidity, provider and/or user dissatisfaction, the political-economic context, and the availability of acceptable and affordable alternatives.

A cut-off level of 25% treatment failures is a widely quoted but somewhat arbitrary figure. Several relatively rich countries in Asia and South America have decided not to accept a level higher than 25%, while in parts of Africa, where malaria is a neglected problem, changes in treatment policies have not occurred until the frequency of treatment failures had reached much higher levels. It has been proposed that the dynamic process of change should be analysed on the basis of the proportion of established clinical failures (14, 97). The various proportions of clinical failure rates have been classified as the grace period, alert period, action period and change period; policy-makers should be informed of the relevance of the available information at all stages.

Grace period—*Low levels of drug failures, ≤ 5%.* Countries can build consensus, conducting a wide range of research studies on the epidemiological, social and behavioural situation, and health systems analysis without urgency. Reliable mechanisms for malaria data

collection and analysis can be established during this period. Baseline data and trends in drug efficacy should be determined.

Alert period—*Treatment failure rates of 6–15%.* Mechanisms for the process of change should be set up and discussions on the rate of change of drug efficacy to the current first-line drug and the timing of any change in policy should be initiated. The expected adverse effects of increased drug resistance should be evaluated.

Action period—*Treatment failures of 16–24%.* Activities to initiate change should commence in accordance with agreed strategies. Ascertainment of treatment failures, potential drug alternatives and channels of drug distribution should be evaluated. This will provide the information needed to prepare a plan for intervention when resistance to the first-line drug becomes intolerable.

Change period—*When the rate of treatment failure has reached 25% or above,* consensus for change must already have been reached so that the change can be made within the shortest period of time possible. The actual cut-off point will depend on many factors as indicated above.

Continuous monitoring and consensus-building is essential to the process leading to change. *In vivo* therapeutic efficacy studies should be conducted throughout the country in order to provide an indication of the geographical pattern of resistance. The tests should be carried out at regular intervals (18 months to 2 years) to provide a longitudinal perspective.

4.7 Process of changing treatment policy: country examples

Ethiopia

In most areas in Ethiopia, 60–70% of cases are due to *P. falciparum* and 30–40% to *P. vivax*. Most of the population have no immunity to the parasite. Chloroquine resistance was first detected in 1986. Although *in vivo* studies conducted between 1991 and 1996 demonstrated increasing resistance to the drug, the methodology used was variable, making comparisons extremely difficult. Following the standardized WHO protocol, a series of *in vivo* studies was undertaken at 18 sites between 1997 and 1998. The total failure rate (ETF plus LTF) for chloroquine was 65%. Evaluation of sulfadoxine–pyrimethamine efficacy at four sites demonstrated an adequate clinical response rate of 92.3%.

Following discussions at the regional and federal levels, the Ministry of Health established a technical working group to develop national guidelines for malaria control. Sulfadoxine–pyrimethamine was considered to be the most appropriate replacement for chloroquine for falciparum malaria; however, it has a low efficacy against *P. vivax*. In 1999 four options were considered by the technical working group for vivax malaria: (i) to leave the treatment of vivax malaria to sulfadoxine–pyrimethamine; (ii) to alternate the use of sulfadoxine–pyrimethamine and chloroquine (*P. vivax* dominates during the dry season, while *P. falciparum* occurs after the rains; (iii) to use a combination of chloroquine and sulfadoxine–pyrimethamine in situations where microscopy is not possible; and (iv) to change from chloroquine to amodiaquine. Option 3 was considered to have potential clinical advantages, although with possible increased adverse effects and costs. Option 4 was excluded as there was 35% resistance to amodiaquine in Ethiopia. It was decided that sulfadoxine–pyrimethamine, the current second-line treatment, should replace chloroquine for laboratory-confirmed cases of *P. falciparum*. Quinine was reserved for the treatment of severe malaria and for second-line treatment of *P. falciparum*, while chloroquine remained the first-line treatment for confirmed cases of *P. vivax* and primaquine would be used for antirelapse treatment of *P. vivax* and for its gametocytocidal activity during epidemics. The

decision was also made to use a combination of chloroquine and sulfadoxine– pyrimethamine as the first-line treatment when laboratory diagnosis was not available. New treatment guidelines were prepared accordingly.

The major challenges for implementation were dissemination of the new recommendations to health workers and ensuring acceptance of the new policy, given human resource and financial constraints. Other challenges were the lack of appropriate protocols for monitoring the therapeutic efficacy and safety of chloroquine + sulfadoxine–pyrimethamine. The main lessons learned in the process of policy change were the need for strong evidence to support the rationale for change, the need for early preparation for change in order to ensure the necessary resources, and the need to involve all stakeholders early in the process. Studies have been planned for measuring the efficacy of chloroquine against vivax malaria and to evaluate the adverse effects of the recommended treatments.

Malawi

Over 85% of the malaria infections in Malawi are due to *P. falciparum*, with *P. ovale* and *P. malariae* accounting for the remainder. In 1978 and 1980, WHO missions found no evidence of chloroquine resistance, but by 1983 clinicians noted increasing slide-confirmed chloroquine-resistant malaria with a rise in admissions for the disease. A malaria control programme was established in 1984 to study chloroquine resistance, identify alternative antimalarial drugs and formulate a rational antimalarial treatment policy. Six sentinel sites were established across the country, and the 7-day WHO *in vivo* efficacy test was used to evaluate chloroquine efficacy. By 1990, parasitological resistance to chloroquine had increased from between 10% and 40% to about 83% in children under 5 years of age. In addition, RIII resistance had increased from 8% in 1984 to 26% in 1990. From 1985 to 1991, the proportion of overall hospital deaths in children under 5 years increased from 10% to 20%.

In December 1991, it was decided that chloroquine would be replaced with sulfadoxine–pyrimethamine as the first-line treatment for uncomplicated malaria in all age groups. At the same time, it was decided to introduce the use of a loading dose for quinine for the treatment of severe malaria and that sulfadoxine–pyrimethamine would be used for intermittent treatment in pregnant women. The new policy was officially launched in March 1993. Delays in implementation were attributed to the time taken for consensus-building and information dissemination among key groups, production of treatment guidelines and information, education and communication materials, and the procurement of adequate stocks of sulfadoxine–pyrimethamine (a challenge as it was more expensive than chloroquine). Antipyretics were used in conjunction with sulfadoxine–pyrimethamine, and chloroquine became a prescription-only drug. However, many people continued to buy branded chloroquine formulations, which remained on sale at pharmacies. Radio and poster messages emphasized that sulfadoxine–pyrimethamine was "stronger" than chloroquine and therefore that only a single dose was needed. As a result, some care-givers were reluctant to use sulfadoxine–pyrimethamine thinking that it may be too strong for young children. Attempts to correct these problems were made using health education including communication through musical and drama groups.

Eight years on, some of these problems are still present. The sulfadoxine-pyrimethamine parasitological failure rate is now about 25% and the treatment failure rate (ETF + LTF) has increased from < 5% in 1991 to a national average of 13% (11–17%). Overall, the Ministry of Health has reported a reduction in deaths and hospital admissions due to malaria as a result of the drug change. Regular sulfadoxine–pyrimethamine efficacy monitoring is continuing.

Peru

Between 1990 and 1997, a major resurgence of malaria occurred in the two most highly endemic areas of Peru, the Northern Pacific Coast and the Amazon region. In response to this resurgence and to clinical evidence suggesting that chloroquine, the first-line treatment for *P. falciparum*, was no longer efficacious, a series of 14-day *in vivo* drug efficacy trials were carried out in both regions, beginning in 1998. These showed RII/RIII resistance levels of > 50% to both chloroquine and sulfadoxine–pyrimethamine at several sites in the Amazon region and > 50% to chloroquine but < 5% to sulfadoxine–pyrimethamine at three sites on the Northern coast. These findings were discussed at a national meeting in August 1999 and it was proposed that the national antimalarial treatment policy should be changed to combination therapy with sulfadoxine–pyrimethamine plus artesunate on the Northern coast and mefloquine–artesunate in the Amazon region, pending studies of the efficacy and safety of both combination therapy regimens. In the meantime, first-line therapy was changed to sulfadoxine–pyrimethamine monotherapy in the north and to a 7-day course of quinine plus tetracycline in the Amazon Basin.

During 2000, 28-day *in vivo* trials comparing sulfadoxine–pyrimethamine monotherapy with sulfadoxine–pyrimethamine plus artesunate combination therapy and mefloquine (15 mg/kg) monotherapy with mefloquine–artesunate combination therapy were conducted. These trials showed efficacy of > 97% with sulfadoxine–pyrimethamine and > 99% with mefloquine monotherapy and with both combination therapies. It is expected that the combination therapies with sulfadoxine–pyrimethamine plus artesunate and mefloquine– artesunate will be introduced as the new first-line treatment for uncomplicated *P. falciparum* malaria on the north coast and in the Amazon region, respectively, by mid-2001.

Rwanda

Antimalarial sensitivity testing was carried out in Rwanda between 1992 and 1997 to investigate complaints from clinicians about therapeutic failures with chloroquine. Although these initial studies showed high levels of chloroquine resistance, the methods used differed between studies and the sites were not thought to be nationally representative. It was decided, therefore, that further studies should be performed using standardized methodology. Rwanda became affiliated to the East African Network for Monitoring Antimalarial Treatment (EANMAT) and used its standardized network test methodology. Four sentinel sites were chosen to represent the ecological and epidemiological profile of the country, two sites in areas of holoendemic stable transmission and two sites in the epidemic-prone areas. The tests demonstrated a chloroquine clinical failure rate of 40% in some sites. It was decided that it was imperative to change the treatment policy. However, it was unclear which drug should replace chloroquine, as the efficacy of sulfadoxine–pyrimethamine in Rwanda was not known and reports from other EANMAT countries showed rapidly increasing resistance to this drug. The decision was therefore taken to test both sulfadoxine–pyrimethamine (at all four sites) and the chloroquine plus sulfadoxine–pyrimethamine combination (at two sites) during 2000. The results indicated that sulfadoxine–pyrimethamine was still efficacious. No significant difference was noted between the efficacy of sulfadoxine–pyrimethamine alone and in combination with chloroquine.

These results suggested that changing to a combination of chloroquine plus sulfadoxine–pyrimethamine did not seem to be a viable option, although a possible justification for its use might be the theoretical reduction of selection pressure on sulfadoxine–pyrimethamine and prolongation of its useful therapeutic life. A review of the antimalarial treatment policy has been scheduled for February 2001. A National Technical Advisory Committee has been formed constituted with representatives from the Ministry of Health, the WHO country office, the National University, the Ministry of Finance and Economic Planning, the Prime Minister's Office and the President's Office, as well as representatives from the health regions to assist in the review.

United Republic of Tanzania

Chloroquine-resistant falciparum malaria has been recognized as a clinical problem in the United Republic of Tanzania since the early 1990s. Monitoring studies conducted at that time indicated the presence of chloroquine resistance. Although over 80% of Tanzanians live close to a source of chloroquine, most acute febrile illness deaths occur at home (48–88%). Of Tanzanians dying with suspected malaria in three districts, 56–80% attended formal health facilities during their final illness. Assuming that treatment guidelines were followed, most would have received chloroquine yet still died. In 1996, the Ministry of Health requested studies to document the level of chloroquine resistance and its geographical distribution. A national monitoring system was established, which became part of EANMAT in 1997.

In 1999, the Tanzanian Task Force on Antimalarial Drug Policy concluded that the clinical treatment failure rate for chloroquine was 52% (range 28–72%), the total treatment failure rate for sulfadoxine–pryimethamine was 9.5% (6.4–34%) and the treatment failure rate for amodiaquine was 4.6% (3.5–6%), and that a change of antimalarial treatment policy was overdue. At present the choice has been: interim introduction of sulfadoxine–pyrimethamine as the first-line antimalarial, with amodiaquine as the second-line, and quinine as the third-line treatment (first choice in severe malaria), supported by a strategy to promote improved utilization of antimalarial drugs and other malaria control measures.

National and subregional data have provided adequate evidence to support a change in first-line antimalarial drug from chloroquine to sulfadoxine–pyrimethamine as an interim measure, anticipating the availability of low-cost, generic combination therapy in the near future. It has been decided that continuous monitoring of treatment efficacy should be maintained and that new developments in potential alternative treatments should be followed carefully and communicated to the policy review group. This new policy will be implemented in 2001. Key lessons learned from the process are the importance of continuous dialogue and consensus-building between the research community, health providers (public and private), policy- and decision-makers and the public.

Viet Nam

Some 40% of the population in Viet Nam live in areas endemic for malaria or with a risk of the disease. For areas with a predominance of *P. vivax* infections and levels of clinically resistant *P. falciparum* of < 50%, chloroquine is still used as the first-line treatment. For other areas, artemisinin or artesunate are used as the first-line treatment. Chloroquine-resistant *P. falciparum*, first detected in 1961, increased during 1980–1990 to 78.2% *in vitro* and 84.6% *in vivo*. Sulfadoxine–pyrimethamine was first used to treat malaria in 1980 but was ineffective by 1986–1990, with a resistance rate of 73.6%. Artemisinin was introduced by the national malaria control programme in 1992.

Monitoring of *P. falciparum* drug susceptibility has been carried out continuously in the country, mainly using 7-, 14-, 21- and 28-day *in vivo* tests. First-line treatments are chosen according to the distribution of drug-resistant *P. falciparum*. In areas with evidence of clinical drug resistance of > 50%, the first-line treatment has been changed. In 1997, the Ministry of Health issued the current guidelines for first-line treatment of malaria for different areas and provincial and district hospitals on the basis of a new survey of the status of drug-resistant *P. falciparum* distribution (1992–1996) and following consultation with a wide range of stakeholders. The guidelines have been distributed to all localities and institutions, and appropriate training has been conducted.

In 2001 it is planned to reconsider the new list of antimalarial drugs and guidelines. CV8, a new antimalarial drug combination containing dihydroartemisinin, piperaquine, trimethoprim and primaquine will be evaluated. There is evidence to suggest that susceptibility of *P. falciparum* to chloroquine may be returning. Further studies are needed to re-evaluate chloroquine in combination with other drugs. It is generally accepted that the antimalarial treatment policy requires reconsideration and possible revision every 3–5 years.

4.8 Policy implementation and access to antimalarial drugs in endemic countries

Implementation

The key aspects of implementation of an antimalarial treatment policy are:

- effectiveness of the proposed treatment; this includes adherence to the treatment as well as efficacy within the real constraints in a health care system,
- financial resources required to implement the policy; these are the resources required by the health sector and by the individual seeking treatment,
- human resources,
- health care infrastructure capacity to implement the policy,
- technical resources,
- awareness-raising and health promotion,
- establishment of effective public-private partnerships,
- education and training of health care staff and other providers,
- education and training of community residents,
- intercountry actions and information exchange to optimize implementation,
- role of the private sector in delivering treatments,
- drug regulation, supply, distribution and quality assurance,
- drug pricing regulations,
- distribution systems,
- monitoring and evaluation of the policy and its impact.

While cost-effectiveness analysis is a useful tool to assist in the allocation of resources, the actual choice of strategy to be implemented is still mainly determined by the ability of individuals and communities to pay the absolute costs of a new drug, i.e. its affordability.

Access

The challenge for a national programme is to ensure that effective antimalarial drugs are easily accessible to the populations at risk of the disease (98). The World Bank African Development indicators define access to health services as the percentage of the population that can reach appropriate local health services (including antenatal care) by local means of transport within one hour. It is estimated that one-third of the population at risk in developing countries lacks access to therapy.

Pharmaceutical "access" is the timely availability of good quality pharmaceuticals to those patients that need them. Many factors determine the level of access: appropriate use, supply management, infrastructure, economic issues, legislation and regulation, manufacturing, and research and development decisions. Access may be defined as:

- physical access,
- financial access (linked to affordability and equity),
- appropriate use of a drug for a defined condition (linked to rational use).

Expanding access to essential medicines requires an understanding of the local epidemiological, economic, regulatory and cultural context. It is a process that requires the participation and support of a range of stakeholders beginning with the government and extending to the private sector. Many access barriers originate in organizational or institutional problems, such as a lack of political will and poor governance, stagnant economic growth or a greater emphasis on secondary versus primary care. In most endemic countries, access of rural communities to health care is constrained by insufficient clinics, pharmacies and health personnel. Some government policy decisions may have a negative impact on pharmaceutical access.

There are four key policy elements that can influence the level of access:

- rational drug selection and use,
- affordability,
- allocation of resources (sustainable financing including insurance schemes and subsidy mechanisms),
- reliable health and supply systems.

These broader issues are critical to the development of rational policies and require extensive debate with a view to arriving at a consensus among all stakeholders on potential solutions. The process must begin with identification of the main factors limiting access and appraisal of potential interventions, the discussion of which is beyond the scope of this document.

5. Conclusions and recommendations

The main conclusions and recommendations agreed at the Informal Consultation are set out below.

5.1 General

1. There are regional differences in patterns of antimalarial drug resistance in countries and policy options should reflect these differences.

2. Previous documentation has suggested that a therapeutic failure rate of $\geq 25\%$ is a useful indicator for change in antimalarial treatment policy. However, it is acknowledged that the decision to change will depend on country circumstances. Because of the time required to implement a change in policy (usually 2–3 years), the evaluation of potential alternatives should begin as soon as failure of the specific drug starts to emerge.

3. It is broadly acknowledged that the options available to countries for improved antimalarial treatment policies are limited, especially in regions of highest resource constraints such as sub-Saharan Africa. In many instances, the lack of resources has resulted in countries continuing the use of drugs whose effectiveness is limited by drug resistance.

4. The potential value of drug combinations, notably those including an artemisinin derivative, to improve efficacy, delay development and selection of drug-resistant parasites and thus prolong the useful therapeutic life of existing antimalarial drugs is widely accepted. Combinations that do not contain an artemisinin derivative could be a preferred option for reasons of cost and accessibility in some countries.

5. Combination therapy could be a viable option for countries that already have widespread resistance of *P. falciparum* to chloroquine, amodiaquine and sulfadoxine–pyrimethamine, provided issues of cost and complexity of implementation can be addressed.

6. Amodiaquine, not recommended for chemoprophylaxis by WHO due to bone marrow and hepatic toxicity following prophylactic use, deserves re-evaluation as a potential therapeutic replacement for chloroquine. It may have particular value as a low-cost component in combination therapy. Results from further clinical trials on safety and efficacy are awaited.

7. Amodiaquine should be given at a therapeutic dose of 30 mg/kg over 3 days (10 mg/kg daily for 3 days) for simplicity of administration in place of the previously recommended 25– 35 mg/kg.

8. The role of intramuscular artemether/arteether as an alternative to intravenous quinine because of simplicity of administration and less frequent dosing schedule in the management of severe malaria in complex emergency situations is re-emphasized.

9. The lack of validated, safe and effective preventive therapies for use in pregnancy in epidemic situations, especially in areas with multidrug-resistant *P. falciparum* was noted and needs to be addressed urgently.

10. Choice of specific options for antimalarial combination therapy for different epidemiological settings, particularly in Africa, was not on the agenda of this meeting. Given the agreed potential of such options, a further technical meeting to review available evidence and make recommendations on antimalarial combination therapy should be convened.

11. Effective antimalarial treatment policies will rely on access to drugs that are significantly more expensive than chloroquine, amodiaquine and sulfadoxine–pyrimethamine. Appropriate political and institutional actions and improved financing are prerequisites to successful advances in this area. These issues deserve immediate serious attention, especially for Africa.

5.2 Future research and other activities

1. There is an urgent need for field research, linked to appropriate pharmaceutical product development, to assess the effectiveness of potential combination therapies that include artemisinin and its derivatives in different epidemiological and health system settings in Africa.

2. The effectiveness of other combinations (not including an artemisinin derivative) with cheaper and already available antimalarial drugs such as 4-aminoquinoline and sulfa drugs for use in Africa should also be explored. This should also be linked to appropriate pharmaceutical product development.

3. Amodiaquine toxicity and its potential cross-resistance with chloroquine require further evaluation as these characteristics may limit the useful therapeutic life of this antimalarial drug.

4. Studies should be conducted to determine whether the continued use of certain drugs as monotherapy will compromise their usefulness as a component of combination therapies.

5. There is an urgent need for more information on and improved options for preventive intermittent treatment in pregnancy and for treatment in complex emergency situations.

6. Studies should be conducted to evaluate the potential of pre-referral use of a single application of rectal artesunate capsules in endemic countries in Africa.

7. Further data are required on factors affecting access to treatment, including health-seeking behaviours, in endemic countries.

8. There is a need for a continuing monitoring system for antimalarial sensitivity patterns, especially in Africa where stronger information bases and inter-country exchanges are required. Efforts should be made to intensify support for resistance monitoring and to develop improved easy-to-use tools, kits and methodologies to facilitate this activity.

9. Sustainable drug discovery and development activities are required to ensure future improvements in malaria chemotherapy.

10. Greater engagement between researchers and decision-makers is essential to ensure that research informs policy and that policy and control needs inform research.

11. Substantial strengthening of health systems is needed to enable them to deliver and promote rationale use and wider access to antimalarial chemotherapy.

A meeting planned for 2001 will address strategy development, resource mobilization and public-private partnerships for improving access to antimalarial drugs.

Part II

Antimalarial Drugs

1. ANTIMALARIAL DRUGS IN CURRENT USE FOR MALARIA PREVENTION AND TREATMENT OF UNCOMPLICATED MALARIA

1.1 CHLOROQUINE

Formulations

- *Tablets containing 100 mg or150 mg of chloroquine base as phosphate or sulfate.*
- *Syrup containing 50 mg of base as chloroquine phosphate or sulfate in 5 ml.*

Efficacy

Chloroquine is a 4-aminoquinoline that has marked and rapid schizonticidal activity against all infections of *P. malariae* and *P. ovale* and against chloroquine-sensitive infections of *P. falciparum* and *P. vivax*. It is also gametocytocidal against *P. vivax*, *P. malariae* and *P. ovale* as well as immature gametocytes (stages 1–3) of *P. falciparum*. It is not active against intrahepatic forms, and should therefore be used with primaquine to effect radical cure of *P. vivax*. and *P. ovale* .

Use

The use of chloroquine as a single first-line drug treatment is now increasingly limited following the evolution of chloroquine-resistant *P. falciparum*, but chloroquine remains the first-line drug of choice in most African countries south of the Sahara where acceptable clinical cure rates can be obtained. In areas where it is still used as a first-line drug, persistent parasitemia and lack of haematological recovery in children may be one of the early signs of chloroquine resistance. Even if the frequency of clinical failures is acceptable in the general population, a more effective first-line treatment may be required for vulnerable groups such as young children and pregnant women. However, the possible desirability of giving different drugs to different population groups must be balanced against logistic and acceptability problems.

In some areas chloroquine use could potentially be extended by its combination with other antimalarial drugs, in order to take continuing advantage of its antipyretic and anti-inflammatory effect and for its action against vivax malaria. This approach has been taken by East Timor, Ethiopia and Papua New Guinea where first-line therapy has been changed to chloroquine plus sulfadoxine–pyrimethamine where no laboratory diagnosis is available. In Uganda, where there is no *P. vivax*, the same combination has recently been advocated because some studies indicated higher efficacy compared with sulfadoxine–pyrimethamine alone.

Resistance of *P. vivax* to chloroquine was first documented in 1989 in Papua New Guinea and is now also confirmed in Indonesia and Myanmar (40, 68, 99–104). Such resistance has only been reported in areas where there is concurrent widespread resistance of *P. falciparum* to chloroquine. Well-documented chloroquine resistance has also been reported in South America (Brazil, Guatemala and Guyana) (41, 105). At present, the situation does not appear to require major changes in national treatment policies. However, it does

require continual monitoring since, in some areas of Indonesia and Papua New Guinea, 20–30% of patients infected with *P. vivax* have recurrences of parasitaemia 1–3 weeks after a course of 25 mg of chloroquine base per kg of body weight. Clinical attacks of chloroquine-resistant *P. vivax* can be treated with mefloquine or quinine.

Recommended treatment

Children and adults for whom the use of chloroquine is indicated, should receive a full treatment dose of 25 mg of chloroquine base per kg given over 3 days. The pharmacokinetically superior regimen consists of 10 mg of base per kg followed by 5 mg/kg 6–8 h later and 5 mg/kg on each of the following 2 days. A more practical regimen used in many areas consists of 10 mg/kg on the first and second days and 5 mg/kg on the third. Both these regimens provide a total dose of 25 mg/kg (e.g. 1 500 mg of base for a 60-kg adult). Details of the dosage schedules for all age groups and according to weight are given in Table 7.

There is no evidence to suggest that increasing the dosage will increase the clinical cure rate in such situations (106) and repeated administration of such high doses may produce adverse reactions.

Table 7. Dosage schedules for chloroquine treatment

Weight (kg)	Age (years)	Number of tablets					
		Tablets, 100 mg of base			Tablets, 150 mg of base		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5–6	< 4 months	0.5	0.5	0.5	0.5	0.25	0.25
7–10	4–11 months	1	1	0.5	0.5	0.5	0.5
11–14	1–2	1.5	1.5	0.5	1	1	0.5
15–18	3–4	2	2	0.5	1	1	1
19–24	5–7	2.5	2.5	1	1.5	1.5	1
25–35	8–10	3.5	3.5	2	2.5	2.5	1
36–50	11–13	5	5	2.5	3	3	2
50+	14+	6	6	3	4	4	2

Recommended chemoprophylaxis

- ***5 mg of base per kg weekly in a single dose,***

or

- ***10 mg of base per kg weekly, divided into 6 daily doses.***

Chloroquine alone is recommended as a prophylactic drug in some of the areas where only *P. vivax* is present (Argentina, Iraq, Syria and Turkey; parts of Bolivia, China, Iran, Peru and Venezuela), or where *P. falciparum* is still sensitive to the drug (Central America north of the Panama Canal, Dominican Republic, Haiti, Tajikistan and parts of Ecuador).

Chloroquine may also be recommended in areas of moderate levels of *P. falciparum* resistance to chloroquine if combined with 200 mg of proguanil daily. This combination provides substantial protection, although less than mefloquine. This regimen is currently recommended for large parts of the Arabian Peninsula and Asia (but not South-East Asia), and in Mauritania, Namibia and part of Colombia.

Pharmacokinetic modelling indicates that the adult dose of 100 mg of chloroquine base daily may be superior to the weekly regimen (107), and a higher efficacy has been found in a retrospective study of travellers taking chloroquine only (108). However, there is a lack of evidence of higher efficacy from comparative studies of the daily compared with the weekly chloroquine regimen when combined with daily proguanil. The daily regimen results in a doubling of the total ingested dose of chloroquine compared with the weekly regimen, and is therefore less suitable for long-term travel because of the risk of adverse reactions (see below). In several countries a combination tablet containing 100 mg of chloroquine base plus 200 mg of proguanil hydrochloride is available, which may increase compliance in adults. Details of the single weekly doses of chloroquine for all age groups and according to weight are given in Table 8.

Table 8. Dosage schedules for chloroquine chemoprophylaxis

		Number of tablets per week	
Weight (kg)	Age (years)	Tablets, 100 mg of base	Tablets, 150 mg of base
5–6	< 4 months	0.25	0.25
7–10	4–11 months	0.5	0.5
11–14	1–2	0.75	0.5
15–18	3–4	1	0.75
19–24	5–7	1.25	1
25–35	8–10	2	1
36–50	11–13	2.5	2
50+	14+	3	2

Use in pregnancy

No abortifacient or teratogenic effects have been reported with chloroquine, so it may be considered safe for treatment or chemoprophylaxis of malaria during pregnancy (109). Although national antimalarial treatment policies in endemic countries may include recommendations for weekly chloroquine chemopro-

phylaxis throughout pregnancy to prevent malaria and its consequences in the pregnant woman and her developing fetus, adherence to this regimen has been very poor.

Drug disposition

Chloroquine is absorbed efficiently when administered orally, peak plasma concentrations being achieved within 3 h (range 2–12 h). The concentration reached in the plasma within 30 min after administration of a single dose of 10 mg/kg is usually substantially greater than the therapeutic level for chloroquine-sensitive *P. falciparum* parasites. The drug has a high capacity for binding to tissues, particularly the melanin-containing tissues of the skin and eye. Binding to plasma proteins, about 50%, is much less than expected from its extensive tissue binding. It is preferentially concentrated in erythrocytes and this concentration is enhanced in parasitized erythrocytes.

Chloroquine is metabolized slowly by de-ethylation of the side chain leading successively to monodesethyl- and bisdesethylchloroquine, followed by de-alkylation. The antimalarial activity and pharmacokinetic profile of desethylchloroquine are similar to those of the parent drug. Chloroquine is eliminated slowly, the parent drug and its metabolites being detected in the blood for up to 56 days with an elimination half-life of around 10 days, depending on the sensitivity of the assay methods used. Chloroquine is predominantly excreted as the parent drug, desethylchloroquine accounting for only about 25% of the total drug excreted (11, 110).

Adverse effects

Serious adverse reactions to chloroquine are rare at the usual antimalarial dosages, but pruritus, which may be intolerable, is common among dark-skinned people. It can sometimes be alleviated by calamine lotion. As pruritus may compromise compliance, it is advisable to use an alternative effective and rapidly acting blood schizonticide in the event of reinfection.

Transient headaches, nausea, vomiting, gastrointestinal symptoms and "blurred vision" may also be experienced following chloroquine administration. This may be avoided by administering the dose after a meal. Attacks of acute porphyria and psoriasis may be precipitated in susceptible individuals. Very rarely adverse events include leukopenia, bleaching of the hair and, extremely rarely, aplastic blood and neurological disorders, such as polyneuritis, ototoxicity, seizures and neuromyopathy.

Irreversible visual impairment resulting from accumulation of chloroquine in the retina is a rare but recognized complication of long-term, high-dosage therapy. Cumulative total doses of 1 g of base per kg body weight or 50–100 g of base have been associated with retinal damage. Retinopathy has rarely, if ever, resulted from doses recommended for malaria chemoprophylaxis (109, 110). Twice-yearly screening for the detection of early retinal changes should be undertaken in anyone who has taken 300 mg of chloroquine weekly for over 5 years and requires further chemoprophylaxis. In travellers who have taken 100 mg daily, screening should be carried out after 3 years. If changes are observed, an alternative drug should be prescribed.

Contraindications

Chloroquine administration is contraindicated in persons:

- with known hypersensitivity,
- with a history of epilepsy,
- suffering from psoriasis.

Overdosage

Chloroquine has a low safety margin. Acute chloroquine poisoning is extremely dangerous and death may occur within a few hours. Poisoning may result after oral ingestion by adults of a single amount of 1.5–2.0 g, i.e. 2–3 times the daily treatment dose. Symptoms include headache, nausea, diarrhoea, dizziness, muscular weakness and blurred vision, which may be dramatic with loss of vision. However, the main effect of overdosage is cardiovascular toxicity with hypotension and cardiac arrhythmias progressing to cardiovascular collapse, convulsions, cardiac and respiratory arrest, and death.

If the patient is seen within a few hours of the event, emesis must be induced or gastric lavage undertaken as rapidly as possible. If not, treatment is symptomatic and directed particularly to sustaining cardiovascular and respiratory function.

1.2 AMODIAQUINE

Formulations

- *Tablets containing 200 mg of amodiaquine base as hydrochloride or 153.1 mg of base as chlorohydrate.*
- *Suspension containing 10 mg of amodiaquine base as hydrochloride or chlorohydrate per ml.*

Efficacy

Amodiaquine is a 4-aminoquinoline antimalarial drug similar in structure and activity to chloroquine. Like chloroquine, it also possesses antipyretic and anti-inflammatory properties.

A systematic review of relevant studies on the treatment of uncomplicated falciparum malaria conducted over the past ten years in Africa showed that amodiaquine proved significantly more effective than chloroquine in clearing parasites, with a tendency for faster clinical recovery. This difference was also observed in areas with considerable chloroquine resistance (30, 111, 112). Data from Cameroon demonstrate better activity of 35 mg/kg than of 25 mg/kg in chloroquine-resistant malaria. However, there is no conclusive evidence that doses of > 25 mg/kg are associated with either improved efficacy or increased toxicity. Amodiaquine also exhibited faster fever clearance times than sulfadoxine–pyrimethamine although the two drugs were equally effective at parasite clearance by day 7, and sulfadoxine–pyrimethamine was more effective on days 14 and 28. This may be related to the slower antimalarial action of the combination and the antipyretic effect of amodiaquine (113, 114).

The efficacy of amodiaquine in the treatment of chloroquine-resistant vivax malaria has not been adequately investigated although a report from Papua New Guinea showed that amodiaquine was more effective than chloroquine for this purpose (28).

Use

In the mid 1980s, fatal adverse drug reactions were reported in travellers using amodiaquine for malaria chemoprophylaxis, even after very few doses (115–118). As a consequence, it was recommended in 1990 that the drug should not be used for chemoprophylaxis or even as an alternative treatment for chloroquine failures (110). However, at its nineteenth meeting the WHO Expert Committee on Malaria did not totally accept this recommendation, stating that amodiaquine could be used for treatment if the risk of infection outweighs the potential for adverse drug reactions (119).

Although global use of amodiaquine has declined owing to the reports of adverse reactions (115, 116, 120–124), some countries have continued to use it as first-line treatment. During this period, there have been no reports of severe adverse effects following such treatment. Many of the data collected on amodiaquine toxicity that led to its withdrawal were from case reports (116, 120–122) in patients with an average age of over 40 years and more (122). Of the published reports in patients with agranulocytosis and toxic hepatitis (115, 116), mean doses of two to three times the recommended therapeutic doses were used over an average period of 9 weeks (125). Evidence has thus accumulated, particularly in Africa (using 35 mg/kg amodiaquine in West Africa) that supports the use of amodiaquine in the treatment of uncomplicated falciparum malaria (126, 113), with the provision that monitoring of efficacy and toxicity are continued (30, 125, 127). It has been suggested that amodiaquine is less toxic than sulfadoxine–pyrimethamine in HIV-positive patients (83).

Studies in East Africa, where there is widespread, intensive resistance to chloroquine and 20–25% of patients treated with amodiaquine have recrudescences of parasitaemia by day 14, have raised concerns that the useful therapeutic life of amodiaquine could be curtailed by partial cross-resistance with chloroquine (30).

Amodiaquine has the advantage over chloroquine of being more palatable and therefore easier to administer to children.

Recommended treatment

Amodiaquine is administered over 3 days at total doses ranging between 25 mg and 35 mg of amodiaquine base per kg in dosage regimens similar to those for chloroquine. At present there is no evidence that the higher doses are associated with either improved efficacy or increased toxicity. A regimen of 10 mg of amodiaquine base per day for 3 days (total dose 30 mg/kg) is recommended as it may offer the advantage of simplicity. Details of the schedules for all age groups are given in Table 9.

Table 9. Dosage schedules for amodiaquine treatment

Weight (kg)	Age (years)	Number of tablets					
		Tablets, 153 mg of base			Tablets, 200 mg of base		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5–6	< 4 months	0.5	0.5	0.25	0.5	0.25	0.25
7–10	4–11 months	1	0.5	0.5	0.5	0.5	0.5
11–14	1–2	1	1	1	1	0.5	0.5
15–18	3–4	1.5	1	1	1	1	1
19–24	5–7	1.5	1.5	1.5	1.5	1	1
25–35	8–10	2.5	2.5	2	2	2	1.5
36–50	11–13	3	3	3	3	2	2
50+	14+	4	4	3	3	3	3

Chemoprophylaxis

Amodiaquine is no longer recommended for chemoprophylaxis because of the risk of severe adverse reactions (see below).

Use in pregnancy

There is no evidence to contraindicate the use of amodiaquine for treatment of malaria during pregnancy.

Drug disposition

After oral administration, amodiaquine is rapidly and extensively metabolized to a pharmacologically active metabolite, desethylamodiaquine, the parent compound being detectable for no longer than 8 h (124). Desethylamodiaquine is concentrated in erythrocytes and is slowly eliminated with a terminal elimination half-life of up to 18 days.

Adverse effects

Adverse reactions to the standard doses of amodiaquine used for malaria treatment are generally similar to those to chloroquine, the most common being nausea, vomiting, abdominal pain, diarrhoea and itching; a less common effect is bradycardia (B. Ngouesse et al., unpublished data, 2000). There is some evidence that itching may be less common with amodiaquine than with chloroquine.

In contrast to chloroquine, however, amodiaquine can induce toxic hepatitis and fatal agranulocytosis following its use for malaria chemoprophylaxis. Data suggest that, in United Kingdom travellers, the incidence of serious reactions for this use of the drug was 1 in 1 700. Blood disorders occurred in 1 in 2 200 travellers and serious hepatic disorders in 1 in 15 650. Fatal events occurred in 1 in 15 500 travellers (122). The toxicity of amodiaquine seems to be related to the immunogenic properties of the quinone imine produced by auto-oxidation of the parent drug (123, 128).

Contraindications

Amodiaquine is contraindicated:

- in persons with known hypersensitivity to amodiaquine,
- in persons with hepatic disorders,
- for chemoprophylaxis.

Overdosage

The acute toxicity of amodiaquine appears to differ from that of chloroquine. Large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions and involuntary movements (58). There are no reports of cardiovascular symptoms following overdose of amodiaquine but intoxication with amodiaquine is far less common than is the case with chloroquine.

1.3 ANTIFOLATE DRUGS

The only useful combinations of antifolate drugs for the treatment of malaria are synergistic mixtures that act against the parasite-specific enzymes, dihydropteroate synthetase and dihydrofolate reductase. Available combinations include the sulfa drug–pyrimethamine combinations sulfadoxine–pyrimethamine and sulfalene–pyrimethamine, the former being more widely available.

Cotrimoxazole, the co-formulated combination of sulfamethoxazole and trimethoprim, has weak antimalarial properties because trimethoprim has a much lower affinity than pyrimethamine for the parasite dihydrofolate reductase enzyme (129). Cotrimoxazole should not be used for the treatment of malaria.

The use of sulfa drug–pyrimethamine combinations for chemoprophylaxis is no longer recommended because of the risk of severe skin reactions.

Formulations

Sulfadoxine–pyrimethamine:

- *Tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.*
- *Ampoules containing 500 mg of sulfadoxine and 25 mg of pyrimethamine in 2.5 ml of injectable solution.*

Sulfalene–pyrimethamine:

- *Tablets containing 500 mg of sulfalene and 25 mg of pyrimethamine.*

Efficacy

Sulfa drug–pyrimethamine combinations are highly active blood schizonticides against *P. falciparum* but are less effective against other Plasmodium species. There is no cross-resistance with the 4-aminoquinolines, mefloquine, quinine, halofantrine or the artemisinin derivatives. The combinations do not have gametocytocidal activity but have been shown to be sporontocidal in animal models.

The long half-life of sulfa drug–pyrimethamine combinations provides a potent selective pressure for parasite resistance in areas of high transmission. In Africa since the late 1980s, *P. falciparum* sensitivity has decreased, particularly in East Africa where sulfadoxine–pyrimethamine has been used on a large scale (130–132), and resistance is demonstrable in parts of West Africa (133). At

present parasitological failure rates on day 7 range from an average of 13% in Malawi, where sulfadoxine–pyrimethamine has been the first-line drug for the treatment of *P. falciparum* since 1993 (134), to around 50% at one site in the United Republic of Tanzania, where pyrimethamine was formerly used for chemoprophylaxis. The corresponding clinical failure rates for sulfadoxine–pyrimethamine are < 5% in Malawi and 6.4–34% (mean 9.5%) in the United Republic of Tanzania (135). The efficacy of sulfadoxine–pyrimethamine treatment is being monitored regularly in Kenya, Uganda and United Republic of Tanzania at eight sentinel sites in each country using the WHO therapeutic efficacy test protocol (29). The ACR for sulfadoxine–pyrimethamine treatment throughout the subregion varies from 66% to 100% (East African Network for Monitoring Antimalarial Treatments, unpublished data, 2000).

In the Amazon Basin of South America and most areas of South East Asia, *P. falciparum* resistance to sulfadoxine–pyrimethamine combinations has rapidly followed their introduction (within 5 years) and now precludes their use in almost all of these areas. These combinations remain effective along the Pacific coast of South America. Sulfa drug-pyrimethamine combinations have low efficacy against *P. vivax* (136). The combination of sulfa drug-pyrimethamine plus chloroquine can therefore be used, not because of a hypothetical effect on the development of resistance, but because it offers an inexpensive and effective option for treatment in areas where chloroquine-resistant, sulfa drug-pyrimethamine-sensitive *P. falciparum* and chloroquine-sensitive *P. vivax* co-exist. For example, Ethiopia (137) and Papua New Guinea, countries where these two Plasmodium species are found together, have recently chosen sulfadoxine–pyrimethamine plus chloroquine as first-line treatment for clinically diagnosed malaria. Such combinations may, however, increase the risk of adverse skin reactions (109).

Use

Sulfa drug–pyrimethamine combinations have been successfully used in areas with highly developed *P. falciparum* resistance to chloroquine and during malaria epidemics. Compliance is high since they offer single-dose therapy. Sulfadoxine–pyrimethamine is the most widely used formulation, sulfalene–pyrimethamine has been largely used in the Indian subcontinent. It is generally assumed that these two formulations are equipotent although there are no comparative data to support this assumption.

There is evidence that folic acid, even in physiological doses, administered concurrently with sulfadoxine–pyrimethamine, can antagonize the action of sulfadoxine (138). It has been suggested that folic acid supplements should be delayed for one week after sulfa drug–pyrimethamine treatment to avoid an inhibitory effect on antimalarial efficacy. However, there are as yet no clinical data to substantiate this.

Recommended treatment

Sulfadoxine–pyrimethamine and sulfalene–pyrimethamine are recommended as single adult doses of 1500 mg of sulfa drug plus 75 mg pyrimethamine (25 mg of the sulfa component per kg as a single dose). This comprises 3 tablets. Details of the dosage schedules for all age groups are given in Table 10.

Sulfadoxine–pyrimethamine dosage should be based on the weight of the patient. In situations where weight cannot be obtained, dosage should at least be based on age.

The following table has been drawn up as the result of a joint effort between field experts and WHO. A weight-for-age data set from WHO containing weight relative to age from children and adults in developing countries only was used. Prior to analysis, the weight-for-age data set was standardized by age and sex to represent the age distribution of a typical population of a developing country. Several combinations of age cut-offs were compared using the proportion that would receive an adequate dose, less than the minimum dose and more than the maximum dose as the primary end-point. The data were weighted for "malaria risk", with young children contributing relatively more to the analysis than adults (16; F. Ter Kuile, personal communication, 2000)

Table 10. Dosage schedules for sulfadoxine–pyrimethamine treatment based on the assumption that quarter tablets are available[a]

		Single dose treatment	
Weight (kg)	Age (years)	Number of tablets	Intramuscular injection (ml)
5–10	2–11 months	0.5	1.25
10.1–14	1–2	0.75	1.90
14.1–20	3–5	1	2.50
20.1–30	6–8	1.5	3.75
30.1–40	9–11	2	5.00
40.1–50	12–13	2.5	6.25
> 50	14+	3	7.50

[a]Reference population using weight and age from 137 000 persons, mostly from Africa (89%) and Asia (11%) (F. Ter Kuile, personal communication, 2000).

Chemoprophylaxis

Sulfa drug–pyrimethamine combinations are no longer recommended for chemoprophylaxis in travellers because of the risk of severe adverse reactions (see below).

Use in pregnancy

Studies in Kenya and Malawi have shown that administration of a full adult treatment dose of sulfadoxine–pyrimethamine given at the first attendance at an antenatal clinic during the second trimester of pregnancy and repeated once at the beginning of the third trimester is effective in clearing or preventing placental infection and peripheral parasitaemia with *P. falciparum* and reducing the risk of low birth weight (51, 53, 139, 140). Several national malaria control programmes in Africa have adopted this intermittent regimen for the prevention of malaria during pregnancy.

There is no clinical evidence that the use of sulfa drug–pyrimethamine combinations for malaria treatment in pregnant women has any effect on the fetus (109). Although there is a theoretical risk of jaundice among premature

babies born to mothers given sulfa drugs late in the third trimester, there does not appear to be an increased risk of kernicterus (141, 142).

Both pyrimethamine and sulfadoxine are excreted in small amounts in breast milk. Pyrimethamine is considered safe during breastfeeding. Diarrhoea and rash have been reported in nursing infants exposed to sulphonamides through breast milk; however, these reports are rare, amd more serious adverse reaction have not been documented. Thus, sulphonamide excretion in breast milk does not appear to pose a significant risk for risk for most infants.

Drug disposition

Sulfadoxine, sulfalene and pyrimethamine are highly bound to protein with relatively long mean elimination half-lives of around 180 h, 65 h and 95 h, respectively (143, 144). Pyrimethamine is extensively metabolized whereas only a small proportion of sulfadoxine is metabolized to acetyl and glucuronide derivatives. Excretion is mainly in the urine. All three drugs cross the placental barrier and are also detected in breast milk.

The mean elimination half-life of pyrimethamine has been reported to be as short as 23 h in patients with acquired immunodeficiency syndrome (AIDS) (83).

Adverse effects

Sulfa drug–pyrimethamine combinations are generally well tolerated when used at the recommended doses for malaria therapy. The most serious events are associated with hypersensitivity to the sulfa component, involving the skin and mucous membranes and normally occurring after repeated administration. Serious cutaneous reactions following single-dose treatment with sulfadoxine–pyrimethamine are rare. Of 12 cases of cutaneous events reported to the manufacturer following therapeutic use of the combination, none had received the recommended single dose (Hoffmann-La Roche, personal communication, 1995). However, such events, including life-threatening erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis, have been reported in 1 in 5 000 to 1 in 8 000 people taking the drug for weekly chemoprophylaxis (145). The combination is therefore no longer recommended for prophylactic use. Data on the incidence of serious cutaneous events following sulfalene–pyrimethamine use are lacking.

Cutaneous drug reactions are more common in patients who are HIV positive (83). There is therefore concern that the high prevalence of HIV infection in parts of Africa may result in an increased frequency of sulfa drug-associated toxicity in HIV-positive people treated with sulfa drug–pyrimethamine combinations for a concomitant malaria infection.

There have been isolated reports of a transient increase in liver enzymes as well as hepatitis occurring after administration of sulfadoxine–pyrimethamine. Haematological changes including thrombocytopenia, megaloblastic anaemia and leukopenia have also been observed. These conditions have usually been asymptomatic but, in very rare cases, agranulocytosis and purpura have occurred. As a rule, these changes regress after withdrawal of the drug.

Concomitant or consecutive administration of sulfa drug–pyrimethamine combinations with trimethoprim or sulfa drug–trimethoprim combinations

such as cotrimoxazole may intensify the impairment of folic acid metabolism and related haematological adverse reactions, as well as increasing the risk of severe adverse skin reactions. It should, therefore, be avoided.

Contraindications

The use of sulfadoxine– or sulfalene–pyrimethamine combinations is contraindicated:

- in persons with known hypersensitivity to sulfa drugs or pyrimethamine,
- for chemoprophylaxis,
- in persons with severe hepatic or renal dysfunction (except when benefits exceed the risks involved),
- in infants in the first two months of life.

Overdosage High doses of the combinations are potentially fatal. Symptoms include headache, anorexia, nausea, vomiting, excitation and possibly convulsions and haematological changes. In cases of acute intoxication, induction of emesis or gastric lavage is useful if undertaken within a few hours of ingestion. Convulsions can be controlled with diazepam and blood dyscrasias treated with intramuscular folinic acid.

1.4 PROGUANIL

Formulation *Tablets of 100 mg of proguanil hydrochloride containing 87 mg of proguanil base.*

Efficacy Proguanil is a synthetic biguanide derivative of pyrimidine with a marked effect on the primary tissue stages of *P. falciparum, P. vivax* and *P. ovale*. Its effect on the primary exoerythrocytic forms of *P. malariae* is unknown. It has some causal prophylactic effect against sensitive strains in contrast to the suppressive prophylactic activity shown by pyrimethamine. Proguanil does not affect hypnozoites and therefore does not have antirelapse activity.

Proguanil also exhibits weak blood schizonticidal activity and, while it is not currently used for treatment, a 3-day regimen of a combination of proguanil with atovaquone, a hydroxynaphthoquinone, has been shown to be effective against multidrug-resistant *P. falciparum* in Thailand (146).

Proguanil is a dihydrofolate reductase inhibitor acting primarily through its major metabolite, cycloguanil. Recent evidence suggests, however, that other mechanisms of action may also be involved. For example: the action of proguanil but not cycloguanil with atovaquone is synergistic (147); and poor metabolizers of proguanil, i.e. persons with defective cytochrome P-450 activity, are at no greater risk of prophylactic breakthrough than normal subjects given proguanil (148). In addition, cross-resistance between cycloguanil and pyrimethamine is not absolute, resistance to the two drugs being controlled by different point mutations on the dihydrofolate reductase/thymidylate synthase (DHFR/TS) gene (149, 150). It is known that proguanil has a second, non-antifolate mechanism of action (129) and this may explain the effect of proguanil–atovaquone.

Use

Proguanil is currently used only for chemoprophylaxis (as a combination with chloroquine in areas with a low prevalence of chloroquine-resistant *P. falciparum*) and for treatment of malaria as a component of the combination proguanil– atovaquone. Some studies have shown that it is efficacious for the treatment of *P. falciparum* malaria when given in combination with dapsone (151).

Treatment

Proguanil is not currently used alone for the treatment of malaria.

Recommended chemoprophylaxis

Proguanil is used in combination with chloroquine (see Table 8 above), generally at a daily dose of 3 mg/kg, giving an adult dose of 200 mg per day. Pharmacokinetic profiles indicate, however, that a twice daily dose of 1.5 mg/kg provides plasma levels of proguanil and cycloguanil that should give better protection than single daily doses of 3 mg/kg (152). Compliance may be a problem with twice daily administration. Details of the dosage schedules for all age groups and according to weight are given in Table 11. In areas with moderate levels of *P. falciparum* resistance to chloroquine, the combination of proguanil plus chloroquine provides significantly less protection than mefloquine or doxycycline.

Table 11. Dosage schedules for proguanil chemoprophylaxis

Weight (kg)	Age (years)	Number of tablets per day
5–8	< 8 months	0.25
9–16	8 months–3 years	0.5
17–24	4–7	0.75
25–35	8–10	1
36–50	11–13	1.5
50+	14+	2

Drug disposition

Pharmacokinetic studies on proguanil are limited. Absorption is rapid, peak plasma concentrations of proguanil and its active metabolite, cycloguanil, being achieved within 4 h of administration. The elimination half-life is approximately 16 h (152).

Adverse effects

Proguanil is remarkably safe and few adverse reactions have been observed, although there are reports indicating that mouth ulcers and hair loss may occur following prophylactic use.

Contraindications

The use of proguanil is contraindicated in persons with liver or kidney dysfunction.

Overdosage Gross overdosage gives rise to abdominal pain, vomiting, diarrhoea and haematuria. No specific antidote exists and symptoms should be treated as they arise.

1.5 MEFLOQUINE

Formulations *Tablets containing 274 mg of mefloquine hydrochloride, equivalent to 250 mg of mefloquine base.* The formulation available in the USA contains 250 mg of mefloquine hydrochloride equivalent to 228 mg of mefloquine base. The three commercial preparations currently available show differences in bioequivalence of both mefloquine and its carboxylic acid metabolite as indicated by differences in maximum plasma concentration (C_{max}) and area under the curve (AUC, time–concentration) (153, 154).

Efficacy Mefloquine is a 4-quinoline methanol chemically related to quinine. It is a potent long-acting blood schizonticide active against *P. falciparum* resistant to 4-aminoquinolines and sulfa drug–pyrimethamine combinations. It is also highly active against *P. vivax* and, *P. malariae* and most probably *P. ovale*. It is not gametocytocidal and is not active against the hepatic stages of malaria parasites. Owing to its long elimination half-life and consequent long-lived subtherapeutic concentrations in the blood, the development of resistance is to be expected especially in areas of high transmission. Since the late 1980s, resistance of *P. falciparum* to mefloquine has developed in areas near the borders between Cambodia and Thailand and between Myanmar and Thailand, and > 50% of patients have recrudescences of parasitaemia within 28 days after a dose of 15 mg/kg (155). The sensitivity of *P. falciparum* populations recrudescing after treatment with mefloquine is substantially reduced compared with the original population (156). *P. falciparum* resistance to mefloquine is accompanied by cross-resistance to halofantrine and reduced sensitivity to quinine. In contrast, laboratory studies have shown some increase in the sensitivity of mefloquine-resistant isolates to chloroquine in Thailand (28). High levels of resistance have not been documented outside South-East Asia, although sporadic reports of drug failure and *in vitro* evidence of reduced sensitivity have been reported from Brazil and several countries in Asia, Africa and the Middle East.

Use Mefloquine can be used both for therapy and chemoprophylaxis. It should only be used for therapy following either microscopical or careful clinical diagnosis of *P. falciparum* infections known or suspected to be resistant to chloroquine or sulfa drug–pyrimethamine combinations. It should not be used for treatment where chloroquine or sulfa drug–pyrimethamine combinations are effective because of its potential toxicity, cost and long elimination half-life. In Thailand, introduction of combination therapy with mefloquine and artesunate was temporally associated with a halt in the steady increase in mefloquine resistance that had been observed when mefloquine was used alone (10).

Mefloquine is recommended as a prophylactic drug for travellers to areas with significant risk of chloroquine-resistant falciparum malaria.

Recommended treatment

15 mg or 25 mg of mefloquine base per kg.

For many years, the standard adult dose of mefloquine for treatment of uncomplicated malaria in areas not affected by significant resistance to mefloquine has been 15 mg/kg. When resistance to mefloquine becomes a problem, however, its efficacy can be increased and its practical usefulness extended by a few years by increasing the standard dose to 25 mg of base per kg (157). In addition, recent pharmacokinetic modelling indicates that a dose of 25 mg/kg provides better protection against the selection of resistant strains (158). Optimum solubility and increased bioavailability can be obtained by drinking water before drug administration (159). The bioavailability of mefloquine is also improved if it is taken after food (160).

The 25 mg/kg dosage of mefloquine is associated with greater drug intolerance, especially vomiting in young children. If vomiting occurs within 1 h of drug intake, a full dose needs to be repeated. Later vomiting does not require repeat therapy. Administration of the drug as a split dose at an interval of 6–24 h substantially improves tolerability (161). Oesophagitis following mefloquine ingestion has been reported and highlights the importance of taking mefloquine with ample amounts of water and preferably not just prior to sleeping. The suggestion that drug-related vomiting can be decreased by treatment of febrile children with an antipyretic has not been borne out by additional studies (162).

Table 12. Dosage schedules for mefloquine treatment

		Number of tablets		
		15 mg/kg (base)	25 mg/kg (base)	
Weight (kg)	Age (years)	Single dose	Dose 1	Dose 2
< 5	< 3 months	not recommended[a]	not recommended[a]	
5–6	3 months	0.25	0.25	0.25
7–8	4–7 months	0.50	0.50	0.25
9–12	8–23 months	0.75	0.75	0.50
13–16	2–3	1.00	1.00	0.50
17–24	4–7	1.50	1.50	1.00
25–35	8–10	2.00	2.00	1.50
36–50	11–13	3.00	3.00	2.00
51–59	14–15	3.50	3.50	2.00
60+	15+	4.00	4.00	2.00

[a]Not recommended owing to limited data in this weight/age group.

Recommended chemoprophylaxis

5 mg of mefloquine base per kg weekly, giving an adult dose of 250 mg of base per week.

It is recommended that, whenever possible, mefloquine chemoprophylaxis should be started 2–3 weeks before departure to achieve higher pre-travel blood levels (163, 164), to detect adverse reactions before travel and to allow consideration of alternatives, e.g. doxycycline or chloroquine plus proguanil. Although steady-state blood levels with this regimen are not achieved until week 6 or 7 and many travellers do not begin chemoprophylaxis until 2–3 weeks before departure, the

efficacy of this regimen for chemoprophylaxis does not appear to be compromised; commencing chemoprophylaxis one week before departure did compromise efficacy (P. Schlagenhauf, personal communication, 2000).

Table 13. Dosage schedules for mefloquine chemoprophylaxis

Weight (kg)	Age (years)	Number of tablets per week
< 5	< 3 months	not recommended
5–12	3-23 months	0.25
13–24	2–7	0.5
25–35	8–10	0.75
36–50+	11–14 +	1

A 3-day loading dose of 250 mg/day followed by 250 mg weekly in adults achieves steady-state blood levels very rapidly and may be considered in special circumstances for travellers who will be at high risk of malaria immediately upon arrival in a malarious area (e.g. military groups) but do not have sufficient time for 2–3 pre-travel doses (165). This regimen is associated with a higher incidence of adverse reactions (see below).

Use in pregnancy

Concern has been expressed about the safety of mefloquine use during pregnancy. Cumulative evidence from 1 627 women inadvertently given mefloquine before conception and during pregnancy as well as from clinical trials involving pregnant women has not confirmed initial fears of embryotoxic or teratogenic effects (166). A retrospective analysis of pregnancy outcomes among women living on the Thai-Myanmar border showed that mefloquine treatment during pregnancy may be associated with an increased risk of stillbirths, but no definite conclusions could be drawn. Thus, while mefloquine may be given with confidence for both chemoprophylaxis and treatment during the second and third trimesters of pregnancy, until further information becomes available, it should be used with caution during the first trimester (161, 167). In non-pregnant women of childbearing potential, mefloquine can be prescribed for chemoprophylaxis, but pregnancy should preferably be avoided during and for 3 months after completing chemoprophylaxis. In the case of inadvertent pregnancy, chemoprophylaxis with mefloquine is not considered an indication for pregnancy termination.

Mefloquine is excreted in breast milk in small amounts, the activity of which is unknown (168). Circumstantial evidence suggests that adverse effects do not occur in breastfed infants whose mothers are taking the drug (169).

Drug disposition

Mefloquine is highly protein bound (98% in plasma) and has a long elimination half-life, varying between 10 and 40 days in adults but tending to be shorter in children and pregnant women. The elimination half-life was found to be longer in Caucasians than Africans or Thais, the variations being attributed to differences in lipid stores. The pharmacokinetic parameters of mefloquine are changed in acute falciparum malaria; the drug reaches a higher Cmax, probably due to a contraction of the apparent volume of distribution (169).

The drug shows stereo-specific elimination with a significantly longer half-life of 531 h for (-)-mefloquine compared to 206 h for (+)-mefloquine (170). Mefloquine is extensively metabolized in the liver and mainly eliminated in the faeces.

The main metabolite, carboxymefloquine, appears 2–4 h after drug intake with concentrations surpassing that of the parent drug by the end of the first week. It is eliminated more slowly than the parent drug. The metabolite lacks antimalarial activity but has a similar toxicity profile to the parent compound. Urinary excretion of mefloquine and its metabolites accounts for 13% of the total dose.

Adverse effects

Between 1984, when it was first registered, and the end of 1995, nearly 11 million people were exposed to mefloquine and another 5 million received it in combination with sulfadoxine and pyrimethamine. The use of mefloquine is, however, subject to diverse opinions, particularly related to its safety. The main problem relates to the drug's potential for inducing neuropsychiatric adverse reactions. There have also been concerns that other adverse effects, such as dizziness, may impair the ability of patients performing activities that require a high level of precision; that vomiting may affect treatment efficacy; and that use of the drug during pregnancy and in persons taking cardioactive drugs for other indications may lead to an increased risk of adverse events (see below).

Frequent adverse effects

These include dizziness, mild to moderate nausea, vomiting, diarrhoea and abdominal pain (self-limiting but may be severe in some users).

Vomiting was nearly three times higher in young children receiving treatment with single doses of 25 mg/kg mefloquine than in those given 15 mg/kg. Splitting the higher dose over 2 days (15 mg/kg followed 24 h later with 10 mg/kg) halved the incidence of vomiting (157). Transient post-treatment dizziness was significantly more frequent in patients given 25 mg/kg and took twice as long to resolve (157). Adverse events have been observed in 18.7% of travellers using mefloquine prophylaxis, a similar incidence to those reported following the use of chloroquine or chloroquine plus proguanil (62).

Neuropsychiatric adverse reactions

Between 1985 and mid-1995, Hoffmann-La Roche received reports of a total of 1 574 neuropsychiatric adverse events associated with mefloquine use, irrespective of causal relationship. These included affective disorders, anxiety disorders, hallucinations, sleep disturbances including nightmares and, in a few people, overt psychosis, toxic encephalopathy, convulsions and acute brain syndrome (171–173). The border between the very unpleasant and "serious events" is

difficult to delineate. Risks appear to vary with ethnic groups, rates reported in Caucasians and Africans being higher than those in Asians for unknown reasons (157, 174–176). Risk is highest in people with a neurological or psychiatric history, a third of patients reporting to the manufacturer with convulsions having had a personal or family history of such events (177). More adverse events were reported in females than in males following prophylactic use, which may reflect higher mg/kg dosing (157, 176–178). On the basis of anecdotal reports, alcohol is postulated to exacerbate the risk, but no adverse events occurred in 20 volunteers in a mefloquine–ethanol interaction study (178, 179).

The frequency of neuropsychiatric adverse reactions is reported to be more common following mefloquine treatment than prophylactic use, occurring in 1 in 200 to 1 in 1 200 patients, depending on their ethnic origins (173, 174; F.O. ter Kuile, C. Luxemburger and F. Nosten, unpublished data). The severe events also appear to be dose-related and were found to be seven-fold higher in those persons retreated with mefloquine within one month (165). Symptoms occurred within 3 days in 73% of patients, with only 9% reporting onset 10 days or more after treatment. The majority (78%) reported resolution of symptoms within 3 weeks. Concomitant administration of quinine may increase the risk of serious neuropsychiatric reactions and convulsions (165).

Following prophylactic use, the prevalence of "serious" neuropsychiatric reactions defined according to the definitions of the Council for International Organizations of Medical Sciences (CIOMS) (180–182), has been reported to be relatively low, being in the order of 1 in 10 000 and usually occurring early in the use of the drug (176, 177). Retrospective assessment of these events reported to the manufacturer indicates that 41% of cases experienced symptoms in the first week of chemoprophylaxis, 59% by week two and 78% by the third week. Over 90% of effects occurred during the first five weeks of chemoprophylaxis (176). In one study of Peace Corps Volunteers, in which long-term weekly chemoprophylaxis was continued despite adverse events in several participants, the rate of adverse reactions decreased with time (61).

The use of a loading dose during chemoprophylaxis may increase the risk of adverse reactions. Strange dreams occurred more frequently after three daily loading doses of 250 mg of mefloquine followed by 250 mg weekly, than after weekly chemoprophylaxis when steady state was achieved in 7 weeks. Depressive feelings, which were more frequent with mefloquine than with chloroquine, resolved as chemoprophylaxis continued (165).

A more recent study of British travellers taking mefloquine for chemoprophylaxis suggests that the relative frequencies of adverse reactions vary with the criteria used. The frequency of "serious" adverse events as defined by the CIOMS criteria was two cases for mefloquine and one for chloroquine plus proguanil, each in a population of around 2 300. However, more pronounced differences were observed between the two regimens in self-reported adverse reactions. Neuropsychiatric adverse events categorized by the traveller as "bad enough to interfere with daily activities" (9.2% of users) or "bad enough to seek medical advice" (2.2%) were each about twice as common with mefloquine than with chloroquine plus proguanil, whereas the percentage of patients reporting any adverse reactions was similar in the two groups (approximately 41%) (183).

Cardiovascular effects

Bradycardia and sinus arrhythmia have been consistently reported in up to 68% of patients treated with mefloquine in hospital-based studies (184), but comparative studies show the incidence to be similar to that observed following treatment with chloroquine, halofantrine or artesunate (184–186). No ECG or blood pressure changes were observed in 45 healthy Australian volunteers who received 250 mg of mefloquine weekly for 4 weeks compared to 50 controls (187). Concomitant administration of mefloquine with other related compounds such as quinine, quinidine and chloroquine may, however, produce ECG abnormalities and increase the risk of convulsions. The use of halofantrine after mefloquine causes significant lengthening of the QTc interval (185) and has been linked with three cardiac arrests in patients treated with both drugs. Halofantrine should, therefore, not be used in persons who have recently received mefloquine.

Since the first use of mefloquine, there have been concerns that its co-administration with drugs used to treat cardiovascular disease such as anti-arrhythmic drugs, beta-adrenergic blocking agents and calcium channel blockers as well as antihistamines, tricyclic antidepressants and phenothiazines might lead to severe adverse reactions. Theoretically, concomitant use of mefloquine and such drugs might also contribute to the prolongation of the QTc interval. However, no evidence of such drug interaction has been reported to date and co-medication with such drugs is no longer contraindicated (54, 188).

Rare events

Haematological events have been reported with mefloquine therapy, < 3% of adverse events reported to the manufacturers being blood dyscrasias. Mefloquine causes transient elevation of transaminases but is rarely associated with hepatitis. Three cases of blackwater fever during mefloquine therapy have been reported (189). Rare dermatological events, including one case of Stevens-Johnson syndrome and one case of toxic epidermal necrolysis, have been temporally related to mefloquine exposure in a few individuals with no prior history of a similar event (190–194).

Effects on performance

Dizziness is recognized as a frequent but transient adverse effect of mefloquine use. Four of seven healthy Caucasian volunteers were severely incapacitated for 3–4 days following administration of 25 mg/kg and all experienced light-headedness (195). This led to the concern that chemoprophylaxis with the drug may impair precision movements. There are, however, indications that, if tolerated, mefloquine does not impede performance. No functional compromise was identified in 203 United States Marines exposed to mefloquine prophylaxis (165) or in 23 trainee pilots who received mefloquine at 250 mg/day for 3 days, then weekly for a total 6 weeks (196). However, sleep disturbances and loss of concentration were reported in volunteers given mefloquine, although the incidence of the latter symptom was not statistically significant. Balance and hearing were unaffected by weekly chemoprophylaxis for 16 weeks in 10 healthy Swedish volunteers (197) and no effect was seen on subtle cerebral function, audiometry and supine/erect blood pressure measurement in a placebo-

controlled study of 45 healthy volunteers taking weekly mefloquine (187). Driving, i.e. road-tracking and car-following tests, has also been reported to be unaffected by mefloquine prophylaxis (179). However, in view of the limited data WHO does not recommend the use of mefloquine in persons, such as air pilots and machine operators, involved in tasks requiring fine coordination and spatial discrimination. Any such persons who experience adverse reactions after mefloquine intake should abstain from work (for at least 3 weeks after treatment) until symptoms have fully resolved.

Drug interactions

Concurrent use of quinine can potentiate dose-related adverse reactions to mefloquine (174). This may be related to the fact that higher quinine and mefloquine blood concentrations than expected are observed when both drugs are given concurrently. In general, mefloquine should not be administered within 12 h of the last dose of quinine. Co-administration of mefloquine with tetracyclines or ampicillin also produces higher mefloquine blood concentrations (198, 199).

Contraindications

The use of mefloquine is contraindicated in persons:

- with a history of allergy to mefloquine,
- with a history of severe neuropsychiatric disease,
- receiving halofantrine treatment,
- who have received treatment with mefloquine in the previous 4 weeks,
- performing activities requiring fine coordination and spatial discrimination e.g. air pilots and machine operators.

Overdosage

Induction of emesis and gastric lavage are of value if undertaken within a few hours of ingestion. Cardiac function and neuropsychiatric status should be monitored for at least 1–3 days and symptomatic and intensive supportive treatment provided as required, particularly for cardiovascular disturbances.

1.6 QUININE, QUINIDINE AND RELATED ALKALOIDS

A. QUININE

Formulations

- *Tablets of quinine hydrochloride, quinine dihydrochloride or quinine sulfate containing 82%, 82% and 82.6% quinine base respectively. Quinine bisulfate formulations, containing 59.2% base are less widely available.*
- *Injectable solutions of quinine hydrochloride, quinine dihydrochloride or quinine sulfate containing 82%, 82% and 82.6% quinine base respectively.*

Efficacy

Quinine is normally effective against falciparum infections that are resistant to chloroquine and sulfa drug–pyrimethamine combinations. Decreasing sensitivity to quinine has been detected in areas of South-East Asia where it has been extensively used for malaria therapy. This has occurred particularly when therapy was given in an unsupervised and ambulatory setting with regimens longer than 3 days. In these settings, patient adherence to therapy is low, leading to incomplete treatment; this may have led to the selection of resistant parasites. There is some cross-resistance between quinine and mefloquine, suggesting that the wide use of quinine in Thailand might have influenced the development of resistance to mefloquine in that country (31). Strains of *P. falciparum* from Africa are generally highly sensitive to quinine.

Use

Quinine is still the drug of choice for severe falciparum malaria in most countries. It should only be used for uncomplicated malaria when alternatives are unavailable, for example, in the following situations.

Quinine may be a useful first-line treatment in areas with multidrug-resistant malaria where *P. falciparum* does not respond to chloroquine, sulfa drug–pyrimethamine combinations, and mefloquine. It is usually combined with another drug especially where some degree of quinine resistance may be present, such as in South-East Asia. National drug policy-makers will need to determine whether quinine is a suitable option.

Quinine is a reasonable option for treatment in travellers returning to non-endemic areas who develop malaria, since the drug-resistance pattern of the parasite may not be known and a fully efficacious drug is needed in non-immunes to prevent progression of uncomplicated malaria to severe disease.

Injectable quinine given by the intramuscular route can be a valuable initial treatment for a patient with uncomplicated malaria who is repeatedly vomiting and therefore unable to take oral drugs. Once vomiting has stopped, oral treatment with an appropriate drug should be resumed.

Quinine can be used as a second-line treatment for patients who fail to respond to the standard first-line therapy and/or are hypersensitive to sulfa drugs. When used in this way, quinine should always be accompanied by another drug.

In the first two of the above situations, a prolonged regimen, which is associated with adverse reactions, contributes to poor treatment adherence and low effectiveness. To improve compliance and maintain its efficacy, quinine is usually combined with tetracycline or doxycycline, although these drugs are contraindicated drugs in children and pregnant women (see below). Clindamycin can be used for these groups.

Quinine (generic form) is included on the essential drug list and is widely available and relatively cheap in many countries. Because of its adverse effects (see below), people rarely take toxic dosages. The drug is appropriate for use under the supervision of a qualified person in patients admitted to health care facilities.

Recommended treatment

Quinine can be given by the oral, intravenous or intramuscular routes. Quinine or quinine-containing compounds such as Quinimax® should not be given

alone for the treatment of malaria as short courses, e.g. 3 days, owing to the possibility of recrudescence (200).

When administered to patients with uncomplicated malaria, quinine should be given orally if possible, by one of the following regimens:

• ***Areas where parasites are sensitive to quinine:***

Quinine, 8 mg of base per kg three times daily for 7 days.

• ***Areas where parasites are sensitive to both sulfa drug–pyrimethamine and quinine, and where adherence may be a problem:***

Quinine, 8 mg of base per kg three times daily for 3 days

plus

Sulfadoxine 1 500 mg or sulfalene 1500 mg plus pyrimethamine 75 mg given on the first day of quinine treatment.

• ***Areas with marked decrease in susceptibility of P. falciparum to quinine***

Quinine 8 mg of base per kg three times daily for 7 days

plus

Doxycycline 100 mg of salt daily for 7 days (not in children under 8 years of age and not during pregnancy); a pharmacologically superior regimen would include a loading dose of 200 mg of doxycycline followed by 100 mg daily for 6 days.

or

Tetracycline 250 mg four times daily for 7 days (not in children under 8 years of age and not in pregnancy).

or

Clindamycin 300 mg four times daily for 5 days (not contraindicated in children and pregnancy).

If oral treatment is not possible, the first dose(s) of quinine should be given intravenously by slow infusion in isotonic fluid or 5% dextrose saline over 4 h. If intravenous infusion is not possible, quinine may be given by intramuscular injection, in which case the drug should be diluted to a concentration of 60 mg/ml and divided into two halves, one half being delivered into each anterior thigh. Whenever parenteral quinine is used, oral treatment should be resumed as soon as the patient is able to take it, and continued for the completion of the course.

Loading doses of quinine are recommended in the management of severe malaria as they establish the optimal blood level of the drug within a few hours. These arguments do not apply in the management of uncomplicated malaria when it is usual to give a standard treatment regimen of quinine without the loading dose. Loading doses of quinine should be avoided when mefloquine has been used within the previous 12 h.

Quinine should be used with caution in the elderly in whom it is metabolized less rapidly (201).

Use in pregnancy

Quinine is safe in pregnancy. Studies have shown that therapeutic doses of quinine do not induce labour and that the stimulation of contractions and evidence of fetal distress associated with the use of quinine may be attributable to fever and other effects of malarial disease (110). The risk of quinine-induced hypoglycaemia is, however, greater than in non-pregnant women, particularly in severe disease. Special vigilance is therefore required.

Drug disposition

Quinine is rapidly absorbed when taken orally, and peak plasma concentrations are reached within 1–3 h. The drug is distributed throughout body fluids being highly protein bound. It readily crosses the placental barrier and is found in cerebrospinal fluid. Quinine is extensively metabolized in the liver, has an elimination half-life of 10–12 h in healthy individuals and is subsequently excreted in the urine, mainly as hydroxylated metabolites (202).

Several pharmacokinetic characteristics differ according to the age of the subject, and are also affected by malaria. The volume of distribution is less in young children than in adults, and the rate of elimination is slower in the elderly than in young adults (201). In patients with acute malaria, the volume of distribution is reduced and systemic clearance is slower than in healthy subjects, these changes being proportional to the severity of the disease. Protein binding of quinine is, however, increased in patients with malaria, as a result of the increased circulating concentration of the binding-protein (alpha-1 acid glycoprotein) (203).

Adverse effects

Cinchonism, a symptom complex characterized by tinnitus, hearing impairment, and sometimes vertigo or dizziness, occurs in a high proportion of treated patients. Symptoms appear when the total plasma concentration of quinine is about 5 mg/l, i.e. at the lower limit of the therapeutic range of the drug, which is 5–15 mg/l. The symptoms that are usually reversible generally develop on the second or third day of treatment and alone rarely constitute a reason for withdrawing the drug.

Dose-related cardiovascular, gastrointestinal and central nervous system effects may arise following excessive infusion or from accumulation following oral administration. Severe hypotension may develop if the drug is injected too rapidly (204). Quinine may enhance the effects of cardiosuppressant drugs and should be prescribed with caution in individuals taking drugs such as beta-adrenergic blocking agents, digoxin and calcium channel blocking agents, especially in those with cardiac disease. Enhanced cardiac toxicity may occur if quinine therapy is administered to individuals who have taken mefloquine for malaria chemoprophylaxis.

Hypoglycaemia may be caused by quinine since the drug stimulates secretion of insulin from pancreatic beta-cells. Hypoglycaemia is particularly likely to develop after intravenous infusion of quinine in pregnancy, since beta-cells are more susceptible to a variety of stimuli at that time (202).

Overdosage

A single dose of quinine of > 3 g is capable of causing serious and potentially fatal intoxication in adults, preceded by depression of the central nervous system and seizures. Much smaller doses can be lethal in children. Dysrhythmias, hypotension and cardiac arrest can result from the cardiotoxic action and visual disorders may be severe, leading to blindness in rare cases. Emesis should be induced and gastric lavage undertaken as rapidly as possible.

B. QUINIMAX®

Quinimax® is an association of four cinchona alkaloids: quinine, quinidine, cinchonine and cinchonidine. It was formerly available as tablets of 100 mg, ampoules of 500 mg, 200 mg and 400 mg and suppositories. Each 100 mg tablet contained 96.10 mg of quinine-resorcine bichlorohydrate (59.3 mg of quinine base), 2.55 mg of quinidine-resorcine bichlorohydrate (1.6 mg of quinidine base), 0.68 mg of cinchonine-resorcine bichlorohydrate (0.4 mg of cinchonine base) and 0.67 mg of cinchonidine-resorcine bichlorohydrate (0.4 mg of cinchonidine base). These have been re-formulated and the preparations now available include tablets of 100 mg and 125 mg of base of all the four components, and ampoules of 125 mg, 250 mg and 500 mg of base of all the four components. Suppositories are no longer available.

Quinimax® has been shown to be somewhat more effective than quinine *in vitro* and in animal models, as well as producing somewhat higher plasma levels in humans. A synergistic effect of the association has been claimed but is doubtful. Limited studies show no significant difference between the therapeutic efficacy of Quinimax® and that of quinine (205). Intramuscular injection of Quinimax® is better tolerated than intramuscular injection of quinine dihydrochloride. Quinimax® is used more widely than generic quinine salts in many countries, especially in francophone Africa.

C. QUINIDINE

Quinidine is a distereoisomer of quinine, with similar antimalarial properties. It is available as tablets of 200 mg of quinidine base as the sulfate and as a slow-release formulation (Quinidine SR®). It is slightly more effective than quinine but has a greater cardiosuppressant effect (110). In other respects the toxicity and drug interactions of quinidine are similar to those of quinine.

Recommended treatment

Quinidine is not recommended for routine treatment of uncomplicated malaria. It is a useful drug for parenteral treatment of severe malaria, and may be used instead of quinine in patients with uncomplicated malaria who require an initial dose of parenteral therapy. Dose regimens are similar to those for quinine.

1.7 HALOFANTRINE

Formulations

- *Tablets containing 250 mg of halofantrine hydrochloride equivalent to 233 mg of halofantrine base.*
- *Paediatric suspension containing 100 mg of halofantrine hydrochloride, equivalent to 93.2 mg of halofantrine base, in 5 ml, i.e. 20 mg of salt per ml.*

Efficacy

Halofantrine, a phenanthrene methanol, is a blood schizonticide that is active against all malaria parasites. It is active against *P. falciparum* infections that are resistant to chloroquine and to sulfa drug–pyrimethamine combinations. Early studies indicated that halofantrine was also active against some but not all isolates with reduced susceptibility to mefloquine.

However, recent work in experimental models and *in vitro* with clones or isolates from various regions indicates cross-resistance between mefloquine and halofantrine (206, 207). Halofantrine resistance is easy to produce in laboratory models and is accompanied by increased susceptibility to chloroquine and decreased susceptibility to mefloquine and quinine (208, 209). Halofantrine is not active against gametocytes or the hepatic stages of malaria parasites.

Use

Halofantrine has no place in malaria control programmes because of its high cost, its variable bioavailability, its cross-resistance to mefloquine and the fact that fatal cardiotoxicity has been reported in certain risk groups following standard therapy. It may be used on an individual basis in patients known to be free from heart disease in areas where multiple drug resistance is prevalent and no other effective antimalarial is available.

Consequently, halofantrine should only be available on a prescription basis. It is not recommended for standby treatment. Strict governmental control of its importation, distribution and utilization is recommended.

Recommended treatment

8 mg of halofantrine base per kg in three doses at 6-h intervals *(for adults and children of > 10 kg).*

The standard dose shown above gives a total dose of 24 mg of halofantrine base per kg, equivalent in adults to 1 500 mg of base. For non-immune patients, a second course of therapy one week after the initial treatment is recommended by the manufacturer to ensure complete cure.

Halofantrine is not recommended in children of < 10 kg since data in this weight group are limited. Data on use of the drug in over 100 children of under 2 years of age suggest, however, that the drug is well tolerated (210). Dosage schedules are shown in Table 14.

Table 14. Dosage schedules for halofantrine treatment using tablets or paediatric suspension

Weight (kg)	Age (years)	Number of tablets[a] per dose	Volume of suspension[a] (ml) per dose
< 10	< 1	not recommended[b]	
10–14	1–2	0.5	6.0
15–18	3–4	0.75	7.5
19–22	5–6	0.75	9.5
23–31	7–9	1	–
32–44	10–12	1.5	–
45–	13+	2	–

[a] This dose should be given three times at 6-h intervals.

[b] Not recommended because of limited data in this age group.

The relative absorption of halofantrine increases approximately six-fold in persons ingesting a meal with a high fat content compared with those who have not recently consumed food (211–213), and higher serum levels correlate with longer QTc intervals (214). Since an increase in absorption tends to cause prolongation of the QTc interval, the manufacturer no longer recommends administration of the drug with food.

Chemoprophylaxis

There are no data to support the use of halofantrine for malaria prophylaxis.

Use in pregnancy

Preclinical studies in rodents have demonstrated toxicity in terms of increased frequency of post-implantation embryonic death and reduced fetal body weight at doses in excess of 15 mg/kg per day (215). No teratogenic effects have been reported. Low weight gains of offspring found in animal toxicity studies suggest that halofantrine may be secreted in breast milk. Halofantrine should therefore be avoided during pregnancy and lactation.

Drug disposition

Halofantrine is a lipophilic weak base that is largely insoluble in water. Its systemic absorption from the current formulations is unpredictably variable but increases up to six-fold in the presence of fatty foods (212, 213). The elimination half life varies with the individual but is generally 24–48 h for the parent drug and twice as long for the biologically active desbutyl metabolite. The functional elimination half-life is therefore 4–5 days. The major route of elimination is the faeces (216).

Adverse effects

Adverse effects include nausea, abdominal pain, diarrhoea, pruritis and skin rashes. Prolongation of the QTc interval and rare cases of serious ventricular dysrhythmias (217–219), sometimes fatal (219), have also been reported. The latter have usually occurred in patients receiving higher than recommended doses who had also received recent or concomitant treatment with mefloquine

or were known to have pre-existing prolongation of the QTc interval (185, 214, 220). Convulsive seizures (J. Horton, personal communication, 1995), intravascular haemolysis that compromises renal function (221), and elevation of serum transaminases have also been observed. The relation of the elevation of serum transaminases to medication is unclear since such changes are commonly seen in acute malaria. Values return to normal within one week after treatment.

Up to August 1994, 31 persons with cardiovascular events were reported to the manufacturer, of whom 13 died. Since that date and following the publication of revised guidelines on risk factors, only two additional cases have been reported to the company (J. Horton, personal communication, 1995).

Contraindications

The use of halofantrine is contraindicated in:

- persons with a history of allergy to the drug,
- persons with pre-existing cardiac disease,
- persons with a family history of sudden death or of congenital prolongation of the QTc interval,
- persons who are using other drugs or have a clinical condition known to prolong the QTc interval,
- persons who have received treatment with mefloquine in the previous 3 weeks,
- pregnant women, breastfeeding mothers and children under one year.

Overdosage

There is no experience of acute overdosage with halofantrine. Immediate emesis or gastric lavage is advised. Supportive measures should include ECG monitoring.

1.8 ARTEMISININ AND ITS DERIVATIVES

Artemisinin *(qinghaosu)* is the antimalarial principle isolated by Chinese scientists from *Artemisia annua* L. It is a sesquiterpene lactone with a peroxide bridge linkage. Artemisinin is poorly soluble in oils or water but the parent compound has yielded dihydroartemisinin, the oil-soluble derivatives artemether and arteether, and the more water-soluble derivatives sodium artesunate and artelinic acid. These derivatives have more potent blood schizonticidal activity than the parent compound and are the most rapidly effective antimalarial drugs known. They are used for the treatment of severe and uncomplicated malaria (222). They are not hypnozoiticidal but gametocytocidal activity has been observed (13).

Formulations

A wide variety of formulations for oral or parenteral use or as suppositories are available (see below). China and Viet Nam continue to be the main producers of artemisinin and its derivatives.

Efficacy

The antimalarial activity of artemisinin and its derivatives is extremely rapid and most patients show clinical improvement within 1–3 days after treatment. However, the recrudescence rate is high when the drugs are used in mono-

therapy, depending on the drug dose administered, the duration of treatment and the severity of disease, but not at present on parasite resistance (34–38). Treatment for < 7 days gave unacceptably high recrudescence rates (39). So far there is no confirmed *in vivo* evidence of resistance of *P. falciparum* to artemisinin and its derivatives. The susceptibility of *P. falciparum* strains from the China-Lao People's Democratic Republic and China-Myanmar border areas to various antimalarial drugs have been tested *in vitro*. The results have indicated declining susceptibility of *P. falciparum* to artemisinin derivatives (223).

Under exceptional circumstances, such as when there is a history of an adverse reaction to the combination agent, artemisinin monotherapy may be indicated, but a 7-day course of therapy is recommended and efforts should be made to improve adherence to the treatment. Preliminary results from Africa indicate that combinations of artesunate plus amodiaquine or sulfadoxine–pyrimethamine are highly efficacious, although efficacy may be compromised in areas with moderate to high levels of resistance to sulfadoxine–pyrimethamine (224, 225; P. Olliaro, personal communication)

These compounds are not recommended for use in the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale* since other effective antimalarial drugs are available for this purpose. However, they may be used in the absence of microscopic diagnosis if they are the recommended first-line treatment.

Use in pregnancy

Preclinical studies have consistently shown that artemisinin and its derivatives do not exhibit mutagenic or teratogenic activity, but all of these drugs caused fetal resorption in rodents at relatively low doses of 1/200–1/400 of the LD50, i.e. > 10 mg/kg, when given after the sixth day of gestation (226). Reports on the use of these drugs during pregnancy are limited (227, 228). However, malaria can be particularly hazardous during pregnancy. Artemisinin and its derivatives are therefore the drugs of choice for severe malaria and can be used for treatment of uncomplicated malaria during the second and third trimester of pregnancy in areas of multiple drug resistance (229). Owing to lack of data, their use in the first trimester is not recommended. The inadequacy of current knowledge on the use of these drugs during pregnancy should be understood by prescribers and all such use should, in principle, be monitored. Clinical outcomes of both a successful and adverse nature should be reported to regulatory authorities.

Drug disposition

High-performance liquid chromatography-electron capture detection (HPLC-ECD) and bioassay methods for studying the pharmacokinetics of artemisinin and its derivatives have now been validated. HPLC-ECD detects separately the parent compound and the major metabolite, dihydroartemisinin, whereas bioassays measure total activity, i.e. parent compound plus metabolite(s). Both methods are cumbersome and only a limited number of laboratories have the capability of conducting assays, especially using HPLC-ECD, which requires a reductive-mode electrochemical analysis and must be performed under oxygen-free conditions. An alternative HPLC method that uses ultraviolet detection is somewhat easier and quicker to use. So far, all methods are for plasma only; no

method is available to measure levels in whole blood. With few exceptions, the lower limit of detection of HPLC-based methods is ≤ 5mg/ml.

Oral bioavailability varies with the derivative and is influenced by disease status. All derivatives, but not artemisinin itself are metabolized to a common bioactive metabolite, dihydroartemisinin, at variable rates (230, 231).

Adverse effects

Extensive clinical trials in China, Myanmar, Thailand and Viet Nam demonstrated no acute cardiovascular or other vital organ toxicity. However, animal studies have demonstrated severe neurotoxicity following parenteral administration of very high doses of artemether or arteether. Both drugs produced a unique pattern of selective neuropathy with chromatolysis and necrosis of scattered neurons in vestibular, motor and auditory brain stem nuclei in rats, dogs and rhesus monkeys (232, 233). Such effects have not been observed with oral administration of any artemisinin derivative or with intravenous artesunate. This has led to the suggestion that the effect is related to specific molecules and their route of administration. The cause, however, appears to be due to sustainable high levels of the drugs and their metabolites, which may occur following intramuscular injection, rather than to the route of administration itself (T.G. Brewer, personal communication, 1996).

There is no clinical evidence to date of serious neurotoxicity resulting from the use of any artemisinin drug in humans in prospective studies of more than 10 000 patients or in the more than 2 million persons who have received these drugs (234, 235). In Thailand, full neurological examinations in more than 1 100 patients who had received an artemisinin drug showed no specific pattern of neurological abnormalities. Studies in Thailand and Viet Nam provided no evidence of any brain stem toxicity attributable to artemisinin and artesunate (236, 237). There is some concern about cerebellar dysfunction (238, 239), and prolonged or repetitive treatment with artemisinin and its derivatives, which may occur in areas of high transmission, must be viewed with caution. Additional studies to monitor subtle neurological changes and hearing loss are required, especially in patients undergoing repetitive treatment. Post-marketing surveillance in countries where these drugs are marketed and used is recommended.

A. ARTEMISININ

Formulations

- *Tablets and capsules containing 250 mg of artemisinin (Viet Nam).*
- *Suppositories containing 100 mg, 200 mg, 300 mg, 400 mg or 500 mg of artemisinin (Viet Nam).*

Efficacy

Artemisinin is a sesquiterpene lactone with a peroxide bridge linkage that appears to be responsible for its antimalarial activity. Artemisinin is a potent and rapidly acting blood schizonticide, eliciting shorter parasite clearance times than chloroquine or quinine and rapid symptomatic responses (240).

Artemisinin is poorly soluble in oils or water. Preclinical and clinical studies show that artemisinin is effective against parasites resistant to all other operationally used antimalarial drugs (240). It is not hypnozoiticidal. It reduces gametocyte carriage (13).

Use

To reduce the recrudesence rate and the risk of development of resistance, as well as to improve compliance, artemisinin should preferably be administered in combination with another effective blood schizonticide. The use of artemisinin as monotherapy should be limited to specific indications, such as in patients with a history of adverse reactions to the combination drug. When monotherapy is used, a 7-day course of therapy is recommended and adherence to the treatment should be ensured.

When given as monotherapy to patients with uncomplicated falciparum malaria who have some degree of immunity, a 5-day oral regimen of artemisinin has generally proven to be curative.

Rectal formulations of artemisinin have a potentially important role to play in the treatment of uncomplicated falciparum infections in children who vomit oral medication, and as emergency treatment prior to referral in situations when parenteral antimalarial drugs are not available or cannot be administered. Studies in Viet Nam have shown the latter to be highly efficacious (241, 242).

Recommended treatment

Although oral artemisinin has been widely employed in the treatment of uncomplicated multidrug-resistant falciparum infections (243, 244), very few well-designed dose-finding studies of artemisinin and its derivatives have been published. The dosage schedules indicated below are based on available clinical data, as pharmacokinetic data are still insufficient for formulating treatment regimens. When used as monotherapy, a minimum 7-day course is required owing to the problem of recrudescent infections. If regimens of < 7 days are employed, combination with mefloquine is indicated to prevent such recrudescence. Pharmacokinetic modelling suggests that a mefloquine dose of 25 mg/kg provides better protection against development of resistance in combination therapy regimens than one of 15 mg/kg (N. White, personal communication, 2000).

Monotherapy 20 mg/kg in a divided loading dose on the first day, followed by 10 mg/kg once a day for 6 days.

Combination therapy

20 mg/kg in a divided loading dose on the first day, followed by 10 mg/kg once a day for two more days plus mefloquine (15–25 mg of base per kg) as a single or split dose on the second and/or third day.

In outpatient settings where adherence is questionable, combination with mefloquine (15 mg or 25 mg of base per kg) is indicated. Several clinical trials have shown that this is the most effective treatment of multidrug-resistant *P. falciparum* malaria (245–247). Mefloquine is administered on the second or third day because there is less risk of vomiting once the clinical condition has improved.

Rectal administration

In emergency pre-referral treatment of severe malaria or for patients who cannot take oral medication, artemisinin can be given by rectal administration before referral to hospital or before medication becomes possible (241, 242). This is intended as emergency management of malaria in life-treatening circumstances and may be provided on a presumptive diagnosis of malaria.

A single dose of 40 mg/kg should be given intarectally, then 20 mg/kg 24, 48 and 72 hours later, followed by oral treatment with an effective antimalarial drug.

Chemoprophylaxis There is no rationale at present for using artemisinin for chemoprophylaxis.

Use in pregnancy

Artemisinin can be used for treatment of uncomplicated malaria during the second and third trimester of pregnancy in areas of multidrug resistance (229). Owing to lack of data, use in the first trimester of pregnancy is not recommended (see above).

Drug disposition

Oral artemisinin is rapidly but incompletely absorbed with peak concentrations 1–2 h after administration (248–250). Artemisinin is rapidly metabolized *in vivo* to dihydroartemisinin. The elimination half-life is 2–5 hours (249, 250). Bioavailability with rectal suppository formulations is 30% less than with oral administration, although there is large inter-individual variation. Studies comparing parasite clearance times following oral and rectal administration have led to the conclusion that therapeutic concentrations should be achieved with suppositories (251, 252). Suppositories have been shown to be as effective as parenteral antimalarial drugs in clinical trials for the treatment of severe malaria (241, 242, 253).

Adverse effects

Adverse effects may include headache, nausea, vomiting, abdominal pain, itching, drug fever (254), abnormal bleeding and dark urine. Minor cardiac changes (mainly non-specific ST changes and first degree atrioventricular block) have been noted during clinical trials. These returned to normal after improvement of malaria symptoms. Experience indicates that artemisinin and its

derivatives are less toxic than the quinoline antimalarial drugs, few adverse effects being associated with their use.

Prolonged or repetitive treatment with artemisinin and its derivatives must be treated with caution. Additional studies, which monitor subtle neurological changes and hearing loss, are required especially in patients undergoing repetitive treatment. Post-marketing surveillance is recommended in countries where these drugs are marketed and used .

Contraindications

Artemisinin is not recommended in the first trimester of pregnancy because of limited data.

Overdosage

There is no experience with overdosage with artemisinin.

B. ARTEMETHER

Formulations

- *Capsules containing 40 mg of artemether (China).*
- *Composite tablets containing 50 mg of artemether (China).*
- *Ampoules of injectable solution for intramuscular injection containing 80 mg in 1 ml (China and France), or 40 mg in 1 ml for paediatric use (France).*

Efficacy

Artemether is an oil-soluble methyl ether derivative of dihydroartemisinin. As with artemisinin, it is effective against *P. falciparum* resistant to all other operationally used antimalarial drugs (240). It is not hypnozoiticidal but it reduces gametocyte carriage (13).

Use

As with artemisinin, when artemether is used for the treatment of uncomplicated *P. falciparum* malaria, it should always be administered in combination with another effective blood schizonticide to prevent recrudescence and delay the selection of resistant strains. Monotherapy with oral or intramuscular artemether with a dose of 1–4 mg/kg per day for 3–5 days results in an unacceptable rate of recrudescence (255). The use of artemether as monotherapy should be limited to specific indications, such as in patients with a history of adverse reactions to the combination drug. When monotherapy is used, a 7-day course is recommended and efforts should be made to ensure adherence.

Artemether is not recommended for the treatment of malaria caused by *P. vivax*, *P. ovale* and *P. malariae* since other effective antimalarial drugs are available for this purpose. However, it may be used in the absence of microscopic diagnosis if the compound is the recommended first-line treatment.

Recommended treatment

Because well-designed dose-finding studies of artemether are limited, the dosage schedules outlined below for uncomplicated and severe malaria are based on available clinical data. When used as monotherapy, a minimum 7-day course is required to prevent recrudescence. If regimens of less than 7 days are employed, combination with mefloquine or another effective blood schizonticide is indicated.

Uncomplicated malaria

Monotherapy: 4 mg/kg loading dose on the first day, followed by 2 mg/kg once a day for 6 days.

Combination therapy

4 mg/kg once a day for 3 days, plus mefloquine (15 mg or 25 mg of base per kg) as a single dose or split dose on the second and/or third day.

Where adherence to the treatment is questionable, especially in outpatients, combination with mefloquine is indicated (256, 257). Cure rates of 95–98% have been demonstrated with this combination in multidrug-resistant areas (258). Mefloquine is administered on the second or third day because there is less risk of vomiting once the clinical condition has improved.

Severe malaria

3.2 mg/kg by the intramuscular route as a loading dose on the first day, followed by 1.6 mg/kg daily for a minimum of 3 days or until the patient can take oral therapy to complete a 7-day course. The daily dose can be given as a single injection. In children, the use of a tuberculin syringe is advisable since the injection volume will be small.

Chemoprophylaxis

Similar to artemisinin.

Use in pregnancy

Similar to artemisinin.

Drug disposition

The pharmacokinetics of artemether following oral administration appear to be similar to those for artemisinin with mean peak plasma concentrations and mean plasma half lives of 1–2 h and 2–3 h, respectively (259). The plasma concentrations of artemether are similar in healthy subjects and those with acute uncomplicated malaria. Plasma antimalarial activity is significantly greater with intramuscular administration than with oral use because the first-pass biotransformation is bypassed (260). Bioavailability of artemether following intramuscular administration was increased and clearance reduced in patients with acute renal failure (261).

Adverse effects

Toxicity studies in dogs and rats indicate that dose-dependent and potentially fatal neurotoxic effects may occur after intramuscular injection of artemether at doses higher than those used for malaria treatment (262). These changes can be widespread but mainly affect areas associated with vestibular, motor and auditory functions (232, 233). No similar findings have been reported in humans treated with normal therapeutic doses of artemether.

Contraindications

Similar to artemisinin.

Overdosage

Similar to artemisinin.

C. ARTESUNATE

Formulations

- *Tablets containing 50 mg of sodium artesunate (China, France and Viet Nam) or 200 mg of sodium artesunate (Switzerland).*
- *Ampoules for intramuscular or intravenous injection containing 60 mg of sodium artesunate in 1 ml of injectable solution (China and Viet Nam).*
- *Suppositories of sodium artesunate (China).*
- *Rectal capsules containing 100 mg or 400 mg of sodium artesunate (Switzerland).*

Efficacy

Artesunate, a water-soluble hemisuccinate derivative of dihydroartemisinin, is the most widely used member of this family of drugs. It is unstable in neutral solutions and is therefore only available for injections as artesunic acid. It is effective against *P. falciparum* resistant to all other operationally used antimalarial drugs (240). It does not have hypnozoiticidal activity. It reduces gametocyte carriage rate (13).

Use

As with artemisinin, when artesunate is used for the treatment of uncomplicated *P. falciparum* malaria, it should always be administered in combination with another effective blood schizonticide to prevent recrudescence and delay the selection of resistant strains. The use of artesunate as monotherapy should be limited to specific indications, such as in patients with a history of adverse reactions to the combination drug. When monotherapy is used, a 7-day course of therapy is recommended and efforts should be made to ensure adherence.

Artesunate is not recommended for the treatment of malaria caused by *P. vivax*, *P. ovale* and *P. malariae* since other effective antimalarial drugs are available for this purpose. However, it may be used in the absence of microscopic diagnosis if the compound is the recommended first-line treatment.

Recommended treatment

Giving a dose twice daily offered no advantage over once daily dosing (34). While 7-day regimens have a therapeutic advantage over 5-day regimens, this might be offset by decreased patient adherence to the treatment; recrudescence rates of 50% are reported following 3-day regimens regardless of the dosage used (263, 264). The shorter courses provided higher cure rates when a double dose was given on the first day of treatment or if the drugs were combined with a longer-acting single-dose antimalarial such as mefloquine (254, 263, 265–267). A regimen of 3–5 days of artesunate in combination with mefloquine given either concomitantly or sequentially provides cure rates of nearly 100% (258, 268, 269).

Because well-designed dose-finding studies of artesunate are limited, dosage schedules are based on available clinical data. When used as monotherapy, a minimum 7-day course is required to prevent recrudescence. If regimens of less than 7 days are employed, combination with mefloquine or another effective blood schizonticide is indicated. A once-daily regimen has been shown to have similar parasite and fever clearance times as a twice-daily regimen (270).

Uncomplicated malaria

Monotherapy: 4 mg/kg loading dose on the first day, followed by 2 mg/kg once a day for 6 days.

Combination therapy

4 mg/kg once a day for 3 days, plus mefloquine (15 mg or 25 mg of base per kg) as a single dose or split dose on the second and/or third day (256).

Where adherence to the treatment is questionable, especially in an outpatient situation, combination with mefloquine (15 or 25 mg of base per kg) is indicated (253, 256–258, 270, 271).

Recent studies in Africa have demonstrated that combinations of artesunate (oral administration of 4 mg/kg daily for 3 days) plus a single dose of sulfadoxine–pyrimethamine on the first day are highly efficacious, although efficacy appears to be reduced in areas with pre-existing moderate levels of sulfadoxine–pyrimethamine resistance (225). Other studies have demonstrated the efficacy of combinations of amodiaquine, 25 mg/kg over 3 days, plus artesunate, 4 mg/kg daily for 3 days (P. Olliaro, personal communication, 2000). The impact of the combination of sulfadoxine–pyrimethamine and artesunate on the development of resistance and the level of malaria transmission is being evaluated in a large-scale trial in the United Republic of Tanzania and in southern Africa (South Africa, Swaziland and Mozambique).

Severe malaria

2.4 mg/kg by the intramuscular route followed by 1.2 mg/kg at 12 and 24 h, then 1.2 mg/kg daily for 6 days. If the patient can swallow, the daily dose can be given orally.

2.4 mg/kg intravenously on the first day followed by 1.2 mg/kg daily until the patient can take orally artesunate or another effective antimalarial drug.

Drug disposition

The pharmacokinetics of artesunate following oral administration appear to be similar to those for artemisinin, with mean peak plasma concentrations and mean plasma half-lives of 1–2 h and 2–3 h, respectively. The plasma concentrations of artesunate are more erratic following administration by suppository compared to the intravenous route, but inadequate absorption is unusual (235).

Adverse effects

Prospective clinical studies of more than 10 000 patients, and post-marketing surveillance of over 4 600 patients in Thailand has not shown any serious drug-related adverse reactions.

Rectal administration

In emergency pre-referral treatment of severe malaria or for patients who cannot take oral medication, artesunate can be given by rectal administration before referral to hospital or before oral medication becomes possible (238, 246). This is intended as emergency pre-referral management of malaria in life-threatening

circumstances and may be provided to patients on a presumptive diagnosis of malaria.

A single dose should be given rectally (rectal capsules/suppositories, 10 mg/kg) as soon as possible once a diagnosis of malaria is made. If the rectal capsule is expelled within the first hour, another rectal capsule should be inserted immediately. A second dose might be required 24 h after the first dose if the patient is still unable to take oral medication at that time, and has not been able to access recommended parenteral treatment.

Table 15 indicates the number of rectal capsules to be inserted for each weight category and probable age category by weight. A new 50-mg suppository is being developed by WHO for infants but is not yet available for use.

Table 15. Dosage schedules for artesunate suppositories for malaria treatment

Weight (kg)	Age (years)	Number of 100 mg capsules	Number of 400 mg capsules
10–19	1–5	1	–
20–29	6–7	2	–
30–39	8–12	3	–
40–49	> 12	–	1
50–92	> 12	–	2
> 90	> 12	–	3

There is no information on efficacy in patients with severe and complicated malaria who have organ and systems failure, including renal failure and liver disease. No studies have been undertaken with this formulation in pregnant or lactating women or in patients with diarrhoea.

Rectal artesunate should not be given for the prevention of malaria.

D. DIHYDROARTEMISININ

Formulations

- *Tablets containing 20 mg, 60 mg or 80 mg of dihydroartemisinin (China).*
- *Suppositories containing 80 mg of dihydroartemisinin (China).*

Efficacy

Dihydroartemisinin is the active metabolite of artemisinin and its derivatives. These derivatives have more potent blood schizonticidal activity than the parent compound. Dihydroartemisinin is the most potent antimalarial of this group of compounds but it is also the least stable.

Oral dihydroartemisinin has been shown to be effective in the treatment of multidrug-resistant uncomplicated *P. falciparum* malaria in China, but experience outside that country is limited (227). Recent studies in Thailand demonstrated a cure rate of 90% in 52 patients given 120 mg of dihydro-

artemisinin followed by 60 mg once daily for 7 days, i.e. a total adult dose of 480 mg (S. Looareesuwan, personal communication, 1995).

Dihydroartemisinin does not have activity against hypnozoites. It reduces gametocyte carriage rate (13).

Use

Dihydroartemisinin appears to offer no advantage over artesunate or artemether for the treatment of uncomplicated or severe malaria.

Dihydroartemisinin is not recommended for the treatment of malaria caused by *P. vivax*, *P ovale* and *P. malariae* since other effective antimalarial drugs are available for this purpose. However, it may be used in the absence of microscopic diagnosis if the compound is the recommended first-line treatment.

Recommended treatment

4 mg/kg in a divided loading dose on the first day followed by 2 mg/kg daily for 6 days.

Data on dihydroartemisinin are very limited, but the currently recommended dosage is as shown above. Dihydroartemisinin has been used in combination with mefloquine (153, 272, 273). Short courses of treatment of less than 5 days have higher recrudescence rates (272, 274).

Drug disposition

Oral dihydroartemisinin is rapidly absorbed and has a short elimination half-life although little is known of its metabolism. Peak plasma concentrations are achieved in 1–2 h and the drug disappears from the circulation within 8–10 h.

E. ARTEETHER

Formulations

Ampoules containing 150 mg of arteether in 2 ml of injectable solution (India, Netherlands).

Efficacy

Arteether is the oil-soluble ethyl derivative of dihydroartemisinin. Clinical trials in India have indicated that it is an effective and rapidly-acting drug for the treatment of uncomplicated (275) and severe falciparum malaria (276, 277).

Use

When arteether is used for the treatment of uncomplicated *P. falciparum* malaria, it should always be administered in combination with another effective blood schizonticide to improve its efficacy and delay the selection of resistant strains. A recrudescence rate of 6–14% has been observed with the use of alpha, beta-arteether (275). The use of arteether as monotherapy should therefore be limited to specific indications, such as in patients with a history of adverse reactions to the combination drug. When given as monotherapy, a 7-day course is recommended and efforts should be made to ensure adherence.

Arteether is not recommended for the treatment of malaria caused by *P. vivax*, *P. ovale* and *P. malariae* since other effective antimalarial drugs are available for this purpose.

Recommended treatment

The recommended regimen according to the Manufacturer is:

For adults, 150 mg/day administrated once daily by the intramuscular route for 3 days.

For children, 3 mg/kg per day by the intramuscular route for 3 days.

Drug disposition

Intramuscular arteether has the lowest bioavailability (34%) of all the artemisinin derivatives tested in the rat, with approximately 14% converted to dihydroartemisinin. It has a long elimination half-life (> 20 h) and is more stable and more lipophilic than the other artemisinin compounds.

Adverse effects

Animal studies have demonstrated limited symptomatic and pathological evidence of neurotoxicity following parenteral administration of high doses (8–24 mg/kg per day for 14 days) of either arteether or artemether (232, 264). Both drugs produced a unique pattern of selective neuronopathy with chromatolysis and necrosis of scattered neurons in vestibular, motor and auditory brain stem nuclei in rats, dogs and rhesus monkeys (232, 233).

F. ARTELINIC ACID

Efficacy Artelinic acid is a water-soluble derivative of artemisinin and is thought to be more stable than artesunate in solution (278) thus offering the potential for oral administration. The compound is still under investigation. It is the only preparation undergoing transdermal studies (279).

1.9 PRIMAQUINE

Formulations *Tablets containing 5.0 mg, 7.5 mg or15.0 mg of primaquine base as diphosphate.*

Efficacy Primaquine is an 8-aminoquinoline highly active against the gametocytes of all malaria species found in humans and against hypnozoites of the relapsing malarial parasites, *P. vivax* and *P. ovale*. It is the only drug currently used for the treatment of relapsing malaria, although another 8-aminoquinoline, CDRI 80/53 (bulaquine) has recently completed phase III clinical trials (36) and another, tafenoquine, is still undergoing clinical trials (280). There are geographical variations in the sensitivity of hypnozoites of *P. vivax* to

primaquine. *P. vivax* from India seems to be the most sensitive, while parasites from the southern regions of South-East Asia and Oceania are the least susceptible. Infections in the Americas, the Mediterranean region, and Europe generally appear to have an intermediate sensitivity. The antirelapse effect of primaquine is a function of the total dose rather than the duration of treatment (281). As a gametocytocide for *P. falciparum*, it is effective given in a single dose of 30–45 mg of base (0.5–0.75 mg of base per kg). In Central America, treatment with amodiaquine followed by 5-day (15 mg of base per day) or 1-day (45 mg of base) regimens of primaquine has been shown to reduce significantly the frequency of recurrent *P. vivax* parasitaemia when compared to amodiaquine alone over a 9-month follow-up period (282).

Primaquine has causal chemoprophylactic activity but, until recently this property had not been evaluated under conditions of natural exposure, partially due to the prevailing view that primaquine was too toxic for routine chemoprophylaxis. Studies in Irian Jaya and Kenya have now shown that daily doses of 0.5 mg/kg (30 mg daily in an adult) can be effective in protecting both adults and children against falciparum and vivax infections (60, 283, 284). The drug was well tolerated for one year in adult males who had normal glucose-6-phosphate dehydrogenase (G6PD) levels (283) and in children aged 9–14 years for the study period of 11 weeks (284). Studies are currently under way to investigate the prophylactic use of primaquine in combination with other antimalarial drugs such as doxycycline (285).

Primaquine has also been shown to be active against asexual blood stages of *P. vivax* at doses of 15–30 mg daily for 14 days in studies in Thailand (286, 287). It also has some activity against the asexual blood stages of *P. falciparum*, but only at doses that would be expected to be toxic.

Use

Antirelapse treatment in P. vivax and P. ovale infections.

Antirelapse treatment in *P. vivax* and *P. ovale* infections should be limited to two categories of patients:

- those resident in low or non-transmission areas, and
- those resident in temperate areas with seasonal malaria transmission, where relapses of *P. vivax* infections usually occur 6–12 months after the primary attack.

It is not necessary to provide antirelapse treatment routinely to patients living in endemic areas with unabated transmission. In such cases, a relapse cannot be distinguished from reinfection and such patients should be treated with an effective blood schizonticide for each symptomatic recurrence of parasitaemia.

In areas with seasonal transmission where relapses occur 6-12 months after the primary attack, antirelapse treatment with primaquine can be delayed. This provides an operational advantage in programmes aimed at interrupting transmission since all persons at risk can be treated (mass drug administration) at the end of the transmission season. This will save time and will also catch re-infections in patients who have already been treated. Pregnant patients in whom primaquine is contraindicated, should be treated only after delivery.

As a gametocytocidal drug in P. falciparum infections.

Gametocytocidal treatment is given only for falciparum malaria in areas with low or moderate malaria transmission. Its objective is the elimination of residual gametocytes after effective blood schizonticidal treatment. For this purpose, a single dose of 0.75 mg/kg is used.

Recommended treatment

Antirelapse treatment in P. vivax and P. ovale infections.

Primaquine may be given concurrently with an active blood schizonticide, such as chloroquine, from the first day of treatment. There are geographical variations in the susceptibility of *P. vivax* to primaquine used for antirelapse therapy (see above).

Antirelapse treatment of vivax malaria with primaquine at doses of 0.5 mg/kg for 14 days has been recommended for South-East Asia and Western Pacific countries. This dose level should only apply to areas south of the equator (where the Chesson strain of *P. vivax* occurs). In areas north of the equator, treatment with 0.25 mg/kg for 14 days is sufficient.

It should be noted that the previously recommended 5-day treatment with primaquine was derived largely on the basis of empirical views. The dose of 15 mg/kg given for 5 days exerts little or no antirelapse activity (70, 288, 289).

When possible, G6PD deficiency should be excluded before standard therapeutic doses of primaquine are given as antirelapse therapy. Relatively simple and inexpensive qualitative kits are now available for this purpose. About 10% of black Africans have a mild, self-limited haemolysis with a dosage of 15 mg of base per kg for 14 days. In persons of Mediterranean or Asian origin with a rarer form of G6PD deficiency, a severe, life-threatening haemolysis can occur (290). In patients with the milder form of G6PD deficiency, an intermittent treatment regimen of 0.75 mg of base per kg weekly for 8 weeks may be administered under medical supervision to reduce the risk of haemolysis (291). Patients should be warned to stop treatment and seek medical advice if they have abdominal pain, become weak or pale, or notice darkening of the urine.

Adherence to these antirelapse regimens is often poor. Ideally, the drug should be given under supervision, but this creates enormous operational difficulties for malaria control programmes.

Gametocytocidal drug in P. falciparum infections.

Single dose of 0.75 mg of base per kg base (adults; 45 mg of base); the same dose may be repeated once, one week later.

Gametocytocidal treatment should only be given in association with or following effective blood schizonticidal medication. Primaquine may be given concurrently with the schizonticidal drug but should not be administered until the condition of the patient stabilizes. The primaquine dose is well tolerated and prior testing for G6PD deficiency is not required.

Chemoprophylaxis

Recent studies have demonstrated that in adults a daily prophylactic dose of 30 mg of base taken during exposure and for one day after departure from a malarious area is highly efficacious in preventing *P. vivax* and *P. falciparum* infections (60, 283, 292). Although primaquine is not currently licensed for chemoprophylaxis, plans are under way to seek a change in labelling to include an indication for the prevention of *P. vivax* and *P. falciparum* infections. All persons taking this regimen should be screened for G6PD deficiency. No serious adverse events have been observed in persons using daily primaquine prophylaxis for 16–52 weeks (283).

Use in pregnancy

Primaquine is contraindicated during pregnancy because of the risk of haemolysis in the fetus, which is relatively deficient in G6PD.

Drug disposition

Primaquine is readily absorbed when taken orally but there is a considerable inter-individual variation in pharmacokinetic profile in humans. Peak plasma concentrations occur within 1–3 h, with a plasma half-life of about 5 h. Primaquine is rapidly metabolized in the liver and only a small amount is excreted unchanged in the urine, which suggests extensive intrahepatic recycling. Two major metabolic pathways have been described. One leads to the formation of 5-hydroxyprimaquine and 5-hydroxy-demethylprimaquine, both of which have antimalarial activity and cause methaemoglobin formation. The other pathway results in the formation of N-acetylprimaquine and a desamino-carboxylic acid. The carboxyclic acid metabolite is the major metabolite in humans and does not appear to be active (293).

Adverse effects

Primaquine may cause anorexia. Other adverse effects include nausea, vomiting, abdominal pain and cramps. These symptoms are dose related and are relatively rare at daily doses of up to 0.25 mg of base per kg (15 mg of base daily in an adult). Gastric intolerance can be avoided by administering the drug with food. Primaquine has also been known to cause weakness, uneasiness in the chest, anaemia, methaemoglobinaemia, leukopenia and suppression of myeloid activity.

In chemoprophylaxis trials, a daily dose of 30 mg of base in persons with normal G6PD status showed good safety and tolerance when compared with placebo and other antimalarial drugs (60, 283, 292).

The more severe adverse reactions at higher doses are related to the effect of primaquine on the formed elements of the blood and bone marrow. Primaquine does not normally cause granulocytopenia at the doses recommended for malaria therapy. The haemolytic action of primaquine is increased in subjects with G6PD deficiency. It is usually self-limiting but blood transfusions may be necessary in severe cases (110).

Contraindications

Primaquine is contraindicated in pregnancy and in children under 4 years of age because of the risk of haemolysis. The drug is also contraindicated in conditions predisposing to granulocytopenia, including active rheumatoid arthritis and lupus erythematosus.

Drug interactions

Primaquine should not be administered with any other drug that may induce haematological disorders.

Overdosage Gastrointestinal symptoms, weakness, methaemoglobinaemia, cyanosis, haemolytic anaemia, jaundice and bone marrow depression may occur with overdosage. There is no specific antidote and treatment is symptomatic.

1.10 ANTIBIOTICS USED AS ANTIMALARIAL DRUGS

A. DOXYCYCLINE

Formulations *Capsules and tablets containing 100 mg of doxycycline salt as hydrochloride.*

Efficacy

Doxycycline is derived from and related to oxytetracycline, and has an identical spectrum of activity. It differs from tetracyclines (see below) in that it is more completely absorbed and more lipid-soluble; it also has a longer plasma half-life.

Use

Doxycycline, like tetracyclines, can be used for therapy in combination with quinine in areas where reduced susceptibility to quinine has been reported. Since the costs of tetracycline and doxycycline are equivalent, the once daily regimen of doxycycline offers a considerable operational advantage over tetracycline, which is given four times daily. Doxycycline should not be used alone for the treatment of malaria because of its slow action.

Doxycycline 200 mg of salt given as a daily dose for 5 days in combination with mefloquine or artesunate has been used successfully in Thailand to treat multiresistant uncomplicated falciparum malaria (297).

In contrast to tetracycline, doxycycline can also be used for chemoprophylaxis. Experience with this indication is limited but increasing. Doxycycline prophylaxis is recommended in areas of mefloquine-resistant falciparum malaria and for those visiting high-risk areas who are unable to take mefloquine (294, 295). It has been used successfully for this purpose by United Nations forces in Cambodia and Somalia (296).

As with tetracycline, oesophageal ulceration can be prevented if the oral dose is washed down with copious amounts of water. Other gastrointestinal symptoms can be reduced if doxycycline is taken with a meal. Milk products must be avoided since they reduce absorption.

Recommended treatment *(see also section on quinine)*

In areas with high levels of resistance to quinine:

Quinine 8 mg of base per kg three times daily for 7 days

plus

Doxycycline 100 mg of salt daily for 7 days (not in children under 8 years of age and not during pregnancy); a pharmacologically superior regimen would include a loading dose of 200 mg of doxycycline followed by 100 mg daily for 6 days.

In areas where parasites are sensitive to quinine and adherence to treatment may be a problem:

Quinine 8 mg base per kg three times daily for 3 days

plus

Doxycycline 100 mg of salt daily for 7 days (not in children under 8 years of age and not during pregnancy); a pharmacologically superior regimen would include a loading dose of 200 mg of doxycycline followed by 100 mg daily for 6 days.

This dosage schedule should significantly improve adherence compared to that for quinine plus tetracycline, in which the latter is given four times daily.

Recommended chemoprophylaxis

Doxycyline100 mg of salt daily.

The prophylactic adult dose of 100 mg of salt daily is equivalent to 1.5 mg of salt per kg daily. It is not practical to give fractions of the capsule formulation to children. If tablets are available, those aged 8–13 years can be given fractions of tablets as shown in Table 16. Doxycycline is contraindicated in children under 8 years of age.

Table 16. Dosage schedules for doxycycline chemoprophylaxis

Weight (kg)	Age (years)	Number of tablets per day
< 25	< 8	contraindicated
25–35	8–10	0.5
36–50	11–13	0.75
50+	14+	1

Use in pregnancy

Doxycycline is contraindicated in pregnancy and in nursing mothers since the risks of its use are similar to those with tetracycline (see below).

Drug disposition

Doxycycline is readily and almost completely absorbed from the gastrointestinal tract and absorption is not significantly affected by the presence of food in the stomach or duodenum. Peak plasma concentrations are reached around 2 h after oral administration. Doxycycline is bound to plasma proteins (80–90%) and has a biological half-life of 15–25 h. It is mainly excreted in the faeces. The drug is more lipid soluble than tetracycline and is widely distributed in tissues and body fluids. It is not thought to be accumulated in patients with renal dysfunction although there are some reports of accumulation in renal failure.

Adverse effects

Adverse effects include gastrointestinal irritation, phototoxic reactions (increased vulnerability to sunburn), transient depression of bone growth (largely reversible) and discoloration of teeth and enamel hypoplasia (permanent). Aggravation of renal impairment may occur but is less likely than with tetracyclines.

Contraindications

Doxycycline is contrainidicated in:

- persons with known hypersensitivity to tetracyclines,
- children under 8 years of age,
- pregnant and nursing mothers,
- persons with hepatic dysfunction.

B. TETRACYCLINE

Formulations *Capsules and tablets containing 250 mg of tetracycline hydrochloride, equivalent to 231 mg of tetracycline base.*

Efficacy Tetracycline is a broad-spectrum antimicrobial drug that has potent but slow action against the asexual blood stages of all Plasmodium species. It is also active against the primary intrahepatic stages of *P. falciparum*. The combination of quinine plus tetracycline given over 5–7 days is still highly effective for treatment in areas of multidrug resistance in Thailand if adherence with the regimen can be assured (298).

Use Tetracycline can be used in combination with quinine in the treatment of falciparum malaria to decrease the risk of recrudescence. It should not be used alone for therapy because of its slow action. It is not used for chemoprophylaxis.

Recommended treatment *(see also section on quinine)*

In areas with high levels of resistance to quinine:

Quinine 8 mg of base per kg three times daily for 7 days

plus

Tetracycline 250 mg four times daily for 7 days (not in children under 8 years of age and not in pregnancy)

In areas where parasites are sensitive to quinine and adherence may be a problem

Quinine 8 mg of base per kg three times daily for 3 days

plus

Tetracycline 250 mg four times daily for 5 days (not in children under 8 years of age and not in pregnancy)

Oesophageal ulceration is rare and can be prevented if tetracycline is taken with ample water. Other gastrointestinal symptoms can be reduced if this drug is taken with a meal. Milk products must be avoided since they reduce the absorption of tetracycline.

Use in pregnancy

Tetracycline is contraindicated in pregnancy. It impairs skeletal calcification in the fetus and can result in abnormal osteogenesis and hypoplasia of dental enamel. Tetracyclines cross the placenta and are found in breast milk and, therefore, should not generally be used in nursing mothers. However, in areas where falciparum infections have reduced susceptibility to quinine and are resistant to mefloquine, and more suitable alternatives are not available, the benefits of therapy with quinine and concomitant tetracycline may outweigh the risks.

Drug disposition

Absorption of tetracycline from the gut is always incomplete and can be further impaired by alkaline substances, chelating agents and, particularly, by milk and milk products, as well as aluminium, calcium, magnesium and iron salts. Peak plasma concentrations occur within 4 h with an elimination half-life of about 8 h. Excretion is primarily in the urine, and enterohepatic circulation gives rise to high concentrations in the bile and liver.

Adverse effects

Gastrointestinal effects include epigastric distress, abdominal discomfort, nausea, vomiting and diarrhoea. These are dose-related and can be alleviated by giving smaller doses more often. Long-term administration may result in alteration of the normal intestinal and vaginal bacterial flora and overgrowth of Candida and other bacteria in the bowel and vagina, although this is rare at the doses used for malaria treatment. Ossification disorders, transient depression of bone growth (largely reversible), discoloration of teeth and enamel dysplasia, which may be permanent in children, have been reported. Skin changes may include phototoxic reactions and increased vulnerability to sunburn. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheliosis, glossitis and vaginitis have also been recorded. Pre-existing renal insufficiency may be aggravated. Hypersensitivity reactions occur rarely. Other adverse effects include angioedema, anaphylaxis and pseudo-tumor cerebri.

Degraded tetracycline may cause renal dysfunction indistinguishable from Fanconi syndrome and skin reactions similar to those of lupus erythematosus. Capsules and tablets should therefore be kept in well-closed containers and protected from the light. Time-expired formulations should be discarded.

Contraindications

Tetracycline is contraindicated in:

- persons with known hypersensitivity,
- persons with pre-existing renal or hepatic dysfunction,
- children under 8 years of age,
- pregnant and nursing mothers (see above).

C. CLINDAMYCIN

Formulations

Capsules containing 75 mg, 150 mg or 300 mg of clindamycin base as hydrochloride.

Efficacy and use

Clindamycin is a semi-synthetic antibiotic derived from lincomycin. Like tetracycline, it is an efficient blood schizonticide with a relatively slow action and a similar spectrum of activity. Along with tetracycline and doxycycline, it is an option for use in combination with quinine for treatment of falciparum malaria when decreased susceptibility to quinine has been reported. However, it is more toxic and costly than tetracycline and doxycycline and should therefore only be used when these drugs are contraindicated or unavailable. It should not be used alone for the treatment of malaria because of its slow action. It is not suitable for chemoprophylaxis.

Recent studies have demonstrated high efficacy in 3-day courses of clindamycin in combination with quinine in Africa (299, 300) and in a 7-day course of the same combination in Thailand (301).

Recommended treatment *(see also section on quinine)*

In areas where parasites are sensitive to quinine and adherence may be a problem

Quinine 8 mg of base per kg three times daily for 3 days

plus

Clindamycin 300 mg four times daily for 5 days.

Clindamycin should be administered with food and copious amounts of water.

Use in pregnancy

Unlike tetracycline and doxycycline, clindamycin use has not been reported to cause adverse events in pregnancy, although it does cross the placenta and may be accumulated in the fetal liver. It is also excreted in breast milk but without any apparent effect. Therefore, clindamycin is not contraindicated for malaria therapy in pregnancy although experience in this regard is limited.

Drug disposition

About 90% of clindamycin is absorbed from the gastrointestinal tract, peak plasma concentrations after oral administration being reached in about 1 h. The drug is rapidly hydrolysed to the free base and widely distributed in body tissues and fluids. Over 90% of circulating clindamycin is bound to plasma proteins. The plasma half-life is 2–3 h although this may be extended in neonates and persons with renal impairment. Clindamycin is partly metabolized, probably in the liver, to active and inactive metabolites, but most of the drug is eliminated unchanged in the faeces. Elimination of metabolites is slow over several days.

Adverse effects

Nausea, vomiting, abdominal pain or cramps have been reported and some patients (2–20%) may experience diarrhoea. Pseudomembranous colitis, a

potentially fatal condition caused by *Clostridium difficile* toxin, may develop in some cases. Hypersensitivity reactions, including skin rashes and urticaria, and neutropenia and thrombocytopenia occur rarely.

Clindamycin should be withdrawn if diarrhoea or colitis occurs. Vancomycin in doses of 125–500 mg every 6 h has been used successfully to treat pseudomembranous colitis.

Contraindications

Clindamycin is contraindicated in persons:

- with hypersensitivity to clindamycin or lincomycin,
- with a history of gastrointestinal disease, particularly colitis,
- with severe hepatic or renal impairment.

D. AZITHROMYCIN

Azithromycin belongs to a new class of azalid macrolid antibiotics. It is structurally similar to erythromycin but is better tolerated, has a broader antimicrobial spectrum of action, and provides prolonged tissue levels. It is an efficient blood schizonticide but has a relatively slow action (P. Olliaro, W. Taylor and J. Rigal, personal communication).

No data exist on the use of azithromycin as monotherapy. Two recent combination trials of artemisinin derivatives plus azithromycin for the treatment of *P. falciparum* malaria showed high parasitological failure rates (302, 303).

A large chemoprophylaxis trial in Kenya using 250 mg of azithromycin daily showed a protective efficacy of 80% for *P. falciparum* infections (304). In a similar trial in Indonesia the protective efficacy was 100% for *P. vivax* but was not high enough for *P. falciparum* to warrant further studies (305).

In the absence of further information, azithromycin cannot be recommended for the treatment or chemoprophylaxis of malaria, either alone or in combination.

1.11 ATOVAQUONE–PROGUANIL

Formulations

- *Film-coated tablets containing 250 mg of atovaquone and 100 mg of proguanil hydrochloride (adult strength).*
- *Paediatric tablets containing 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride.*

Efficacy

Atovaquone was originally developed as an antimalarial compound, but was registered for the treatment of opportunistic infections caused by *Pneumocystis carinii* and *Toxoplasma gondii* associated with AIDS. Atovaquone alone has weak antimalarial activity and recrudescence of parasitaemia occurs in one-third of patients with *P. falciparum* when used alone. Such recrudescent parasites are

highly resistant (146). In combination with proguanil, however, a synergistic effect is seen. Atovaquone–proguanil is highly efficacious against *P. falciparum*, including strains that are resistant to chloroquine and mefloquine, with cure rates of 94–100% (144, 306–308).

Limited information exists on the efficacy of this combination against other species of malaria parasites, but it appears to be effective at eliminating blood stage infections. Relapses are common with *P. vivax* infections unless primaquine is given at the same time.

There are no data available on use in children weighing < 11 kg.

Recommended treatment

For adults, 1 g of atovaquone plus 400 mg of proguanil (4 tablets) daily for 3 days.

The manufacturer does not envisage active commercialization of the drug in malaria endemic countries. Instead, a Malarone® Donation Program has been launched with a commitment to provide up to 1 million free treatments annually to national malaria control programmes. This Program has already begun at several sites in Kenya and Uganda. Under the guidelines of the Donation Program, use of the drug is to be restricted to patients who fail to respond to treatment with current first- and second-line drugs.

Active marketing of atovaquone–proguanil is being promoted in non-endemic countries for both treatment and chemoprophylaxis in travellers to malarious areas. The recommended treatment regimens are shown in Table 17.

Table 17. Dosage schedules for atovaquone–proguanil treatment

Weight (kg)	Number of tablets per day (adult strength)	Number of days	Daily dose * atovaquone (A) + proguanil (P)
< 11	not recommended		
11–20	1	3	250 mg A + 100 mg P
21–30	2	3	500 mg A + 200 mg P
31–40	3	3	750 mg A + 300 mg P
> 40	4	3	1000 mg A + 400 mg P

* The manufacturer recommends that the daily dose should be taken with food or a milky drink at the same time each day.

Chemoprophylaxis

For adults, 250 mg of atovaquone plus 100 mg of proguanil (one tablet) daily.

Atovaquone–proguanil offers an alternative for chemoprophylaxis in those persons travelling to chloroquine-resistant *P. falciparum* areas who cannot take mefloquine or doxycycline. The prophylactic dose in adults is one tablet daily beginning one day before entering the malarious area, continuing throughout the stay in the malarious area and for 7 days after leaving. Studies have shown that atovaquone–proguanil has good chemoprophylactic activity in semi-immune persons (309-311), and there are some data on its effectiveness in non-immune

persons (312, 313). Prophylactic dosage schedules for children are shown in Table 18.

Table 18. Dosage schedules for atovaquone–proguanil chemoprophylaxis in children

Weight (kg)	Number of tablets per day (paediatric strength)	Daily dose * atovaquone (A) + proguanil (P)
< 11	not recommended	
11–20	1	62.5 mg A + 25 mg P
21–30	2	125 mg A + 50 mg P
31–40	3	187.5 mg A + 75 mg P

* The manufacturer recommends that the drug should be taken with food or a milky drink at the same time each day.

Use in pregnancy

Atovaquone alone and atovaquone–proguanil are not teratogenic in rats. Proguanil is safe during pregnancy but there is insufficient information on the safety of atovaquone or the combination drug in pregnant or lactating women.

Drug disposition

Atovaquone is absorbed slowly from the gastrointestinal tract and is subject to wide individual variability. Absorption is greatly increased if the drug is taken with a fatty meal. The half-life of atovaquone is approximately 60 h compared with about 15 h for proguanil. There does not appear to be significant metabolism of atovaquone.

Adverse effects

Adverse effects include abdominal pain, nausea, vomiting, diarrhoea, headache, anorexia and coughing.

With the exception of vomiting, the frequency of these symptoms is similar to that seen during acute malarial attacks. During clinical trials, one case of anaphylaxis following treatment with atovaquone–proguanil was observed. In double-blind placebo-controlled chemoprophylaxis trials, the frequency of adverse events was similar to that in the placebo group, indicating that the combination is very well tolerated (310–313).

Contraindications

Atovaquone–proguanil is contraindicated in persons with hypersensitivity to atovaquone and/or proguanil.

It is not recommended at present for use in pregnancy because of lack of data. Caution is indicated in persons with severe renal failure (creatinine clearance < 60 ml/min).

1.12 CHLOROQUINE–PROGUANIL

Formulations *Film-coated tablets containing 161.2 mg of chloroquine phosphate (equivalent to 100 mg of chloroquine base) plus 200 mg of proguanil hydrochloride.*

Efficacy There is no evidence of synergism or pharmacokinetic interaction between chloroquine and proguanil or cycloguanil (314). Although the combination has some activity against strains of *P. falciparum* with low levels of resistance to chloroquine, it is significantly less effective than mefloquine or doxycycline as a chemoprophylactic agent (61, 62).

Use This combination drug was developed for chemoprophylaxis in adult travellers (≥ 15 years of age and ≥ 50 kg body weight) travelling to areas where the combination of chloroquine plus proguanil is recommended. This may include areas in which the response of *P. falciparum* to chloroquine is already somewhat compromised. Owing to the chloroquine component, the combination will also be suppressive against initial infections of *P. vivax*, *P. ovale* and *P. malariae* but does not have antirelapse activity and does not prevent later recrudescences.

Treatment This combination is not recommended for malaria treatment.

Chemoprophylaxis ***One tablet daily (adults).***

Chemoprophylaxis of one tablet daily (315, 316) should start at least 24 h before entering the malarious area and continue until 4 weeks after exposure to malaria transmission has ended.

Use in pregnancy

Chloroquine and proguanil are both considered safe for use in pregnancy.

Drug disposition

There is no evidence of any pharmacokinetic interaction between chloroquine and proguanil in this combination drug.

Adverse effects

There are no apparent toxic interactions between chloroquine and proguanil. The combination therefore has the toxicological properties of the two components (see sections on chloroquine and proguanil). With the daily regimen recommended for chemoprophylaxis, the critical cumulative dose of 100 mg of chloroquine base will be reached in less than 3 years of continuous use.

Contraindications

Chloroquine–proguanil is contraindicated in:

- persons with known hypersensitivity to either proguanil or the 4-aminoquinolines,
- renal insufficiency,
- retinopathy related to earlier use of chloroquine,
- persons undergoing dialysis.

Caution is indicated in persons with impaired liver function, a history of epilepsy, or with severe G6PD deficiency

1.13 ARTEMETHER–LUMEFANTRINE

Formulations *Tablets containing 20 mg of artemether plus 120 mg of lumefantrine (benflumetol).*

Efficacy

Lumefantrine is an aryl amino alcohol similar to quinine, mefloquine and halofantrine. Biochemical studies suggest that its antimalarial effect involves lysosomal trapping of the drug in the intra-erythrocytic parasite, followed by binding to toxic haemin that is produced in the course of haemoglobin digestion. This binding prevents the polymerization of haemin to non-toxic malaria pigment.

A total of 16 clinical trials with more than 3 000 patients, including 600 children under 5 years of age, have been carried out in Europe, South-East Asia and Africa. In areas with low or no malaria transmission, the 28-day cure rates with a 4-dose regimen were 95.1% outside Thailand and 76.5% in Thailand, where most patients came from areas with multidrug-resistant malaria (317–319). In Thailand, a 6-dose regimen gave a 28-day cure rate of 97.3% (318). In a trial in Africa, the 28-day cure rate complemented by PCR studies to distinguish re-infections from recrudescences showed a corrected cure rate of 92.7% (319). A dose-finding trial in Thailand demonstrated the importance of the number of doses rather than the dose level for the efficacy of this combination drug. These studies also showed that the cure rate was 97% in patients receiving a total dose of ≥ 50 mg/kg, regardless of the level of initial parasitaemia, but that cure rates were significantly lower with parasite densities of ≥ 20 000 per ml when the total lumefantrine dose was < 50 mg/kg (320–322).

Use

Artemether–lumefantrine can be used for the treatment of uncomplicated infections with *P. falciparum*, including strains from multidrug-resistant areas. Although the 4-dose regimen appears to be effective in semi-immune adult patients from Africa, children should probably receive a 6-dose regimen because of their lower immunity (323; M. van Vught et al., unpublished data). To avoid confusion and ensure the highest efficacy and reliability with this drug, it may be advisable to recommend the 6-dose regimen uniformly as the standard treatment. Artemether–lumefantrine has been registered in Switzerland for use as standby emergency treatment for travellers to areas where the parasite is resistant to other drugs.

Recommended treatment

In semi-immune patients, the manufacturer recommends the 4-dose regimen, consisting of 1, 2, 3 or 4 tablets taken at 0 h, 8 h, 24 h and 48 h. The total course for an adult is 16 tablets, which gives a total dose of 320 mg of artemether plus 1920 mg of lumefantrine.

In areas with multidrug-resistant *P. falciparum* and in non-immune patients, an intensive 6-dose course consisting of the doses shown above at 0 h and 8 h, and twice daily doses on the next 2 days is recommended, as shown in Table 19.

Thus, the course for an adult would be 4 tablets at 0 h and 8 h and 4 tablets twice a day on the second and third days.

There is no evidence of increased toxicity with the 6-dose as compared to the 4-dose regimen and, for simplicity of implementation, it may be advantageous to use the 6-dose regimen in all areas.

Table 19. Dosage schedules for artemether–lumefantrine treatment

Weight (kg)	Number of tablets per dose (at 0h, 8h, 24h, 36h, 48h and 60h)	Content of artemether (A) + lumefantrine (L) per dose
< 10	not recommended	
10–14	1	20 mg A + 120 mg L
15–24	2	40 mg A + 240 mg L
25–34	3	60 mg A + 360 mg L
> 35	4	80 mg A + 480 mg L

Chemoprophylaxis

This drug is not recommended for chemoprophylaxis.

Use in pregnancy

This drug should not be used in pregnant women. Safety of its use in pregnancy has not yet been established.

Drug disposition

Absorption of lumefantrine is variable and is increased when the drug is taken with food. Maximum blood levels are observed 6–12 h after drug administration. The half-life is 88 h in healthy subjects and about twice as long in malaria patients. The drug is excreted via the liver and faeces. There is no evidence of pharmacokinetic interaction between artemether and lumefantrine (324).

Adverse effects

The following adverse effects have been reported (325): dizziness and fatigue, anorexia, nausea, vomiting, abdominal pain, palpitations, myalgia, sleep disorders, arthralgia, headache and rash.

In children and adults treated with this combination, the frequency and degree of QTc prolongations was lower than with chloroquine, mefloquine or halofantrine (324). Studies show no indication of cardiotoxicity (326).

Contraindications

Artemether–lumefantrine is contraindicated in:

- pregnant and lactating women,
- persons with known hypersensitivity to either of the components,
- persons with severe malaria.

1.14 MEFLOQUINE–SULFADOXINE–PYRIMETHAMINE

The combination of mefloquine–sulfadoxine–pyrimethamine was developed for therapeutic use on the basis of the observation that its components display at least additive activity and that their combination might delay the emergence of parasite resistance (109). It has not been recommended for general use by malaria control programmes for either chemoprophylaxis or treatment since 1990 because of concerns of the risk of severe adverse reactions to the sulfadoxine component, and because it did not appear to be justified to introduce mefloquine on a large scale to areas where sulfa drug–pyrimethamine was still effective. It was considered that its hypothetical effect on the development of resistance in natural human parasite populations could not counter its documented toxicity (110). The use of this drug as a first-line treatment for uncomplicated *P. falciparum* infections in Thailand was temporally associated with a period of rapid development of resistance to mefloquine, perhaps related to the 15 mg/kg dose of mefloquine in the combination (158), the existing high resistance to sulfadoxine–pyrimethamine (327) or the long half-life of mefloquine, which led to a long duration of subtherapeutic concentrations unprotected by sulfadoxine–pyrimethamine (328). As a result, mefloquine resistance developed within six years of deployment of this combination (329, 330).

2. STATUS AND POTENTIAL OF COMBINATION THERAPIES

2.1 Co-administered (non-fixed) combinations used in the past or present

Table 20 shows the status of combinations in this category.

Table 20. Status of co-administered (non-fixed) combinations used in the past or present

Combination	Status
Chloroquine + SP	First-line: current in Ethiopia, Papua New Guinea (≥ 5 years) and Vanuatu; chosen in 2000 by Solomon Islands, Uganda and Zimbabwe.
Amodiaquine + SP	First-line: Colombia, Papua New Guinea (< 5 years).
Quinine + antibiotic	Thailand, Brazil
Mefloquine + artesunate or other artemisinin derivative (333)	First-line: Cambodia, Thailand and Viet Nam.

SP, sulfadoxine–pyrimethamine

Chloroquine or amodiaquine plus sulfadoxine–pyrimethamine:

These combinations have been shown to have higher cure rates than sulfadoxine–pyrimethamine alone (332).

Artemether or lumefantrine:

This combination is currently used as the first-line treatment in KwaZulu Natal, North Province of South Africa.

2.2 Co-administered (non-fixed) combinations under trial involving available drugs

Table 21 shows the status of combinations in this category.

Table 21. Status of co-administered (non-fixed) combinations under trial involving available drugs

Combination	Status
Atovaquone–proguanil + artesunate	Large trial in North West border of Thailand illustrated safety and effectiveness
SP + artesunate	Safety and efficacy trials in progress in Bangladesh, Gambia, Irian Jaya, Kenya, Malawi, Peru and Uganda
Chloroquine + artesunate	Safety and efficacy trials in progress in Burkina Faso, Côte d'Ivoire and Equatorial Guinea
Amodiaquine + artesunate	Safety and efficacy trials in progress in Colombia, Gabon, Kenya and Senegal
Mefloquine + artesunate	Safety and efficacy trial to start in Brazil in 2001

SP, sulfadoxine–pyrimethamine

Sulfadoxine–pyrimethamine plus artesunate

Sulfadoxine–pyrimethamine is expected to fail rapidly in areas of chloroquine resistance in East Africa and more gradually in West Africa. The combination of sulfadoxine–pyrimethamine with artesunate may reduce the rate of emergence of sulfadoxine–pyrimethamine resistance. In two trials in Africa (in Gambia [224, 225] and Kenya) a 3-day artesunate regimen seems to be necessary to optimize treatment efficacy. In Gambia, the effect on gametocyte carriage was similar with either one or three days of artesunate.

It is important to decide whether sulfadoxine–pyrimethamine resistance has progressed too far in parts of Africa to warrant the high cost of implementing artemisinin-based combination therapy that includes sulfadoxine–pyrimethamine (SP ACT). Sulfadoxine–pyrimethamine resistance is strongly associated with mutations in parasite *dhfr*, the gene that encodes parasite dihydrofolate reductase (DHFR) (333–335). While three mutations are now common in many parts of Africa (333, 336), a fourth mutation, providing complete resistance to sulfadoxine–pyrimethamine, has not been reported, although codon 164 mutations may already exist at low frequency (337). Using epidemiological modelling, it is possible that SP ACT will still delay the rate of selection of the quadruple mutant, if implemented widely before this genotype becomes prevalent (IM Hastings, WM Watkins, NJ White, unpublished data). However, *dhfr* triple mutant infections would still be common, requiring treatment with SP ACT, since this genotype is of borderline susceptibility to sulfadoxine–pyrimethamine (338). It is debatable whether, with this background of sulfadoxine–pyrimethamine resistance, SP ACT should be used (with all its implications) or whether other more efficacious combinations should be introduced. Candidates include amodiaquine ACT, artemether–lumefantrine and ACTs under development e.g. LapDap ACT.

It is important to take into consideration the fact that it would be extremely difficult to eliminate sulfadoxine–pyrimethamine monotherapy from the market as it is cheap, well-known and produced by many generic drug producers.

Amodiaquine plus artesunate

The 3-day regimen of both components is currently co-administered although co-formulation is feasible. Amodiaquine has a greater efficacy than chloroquine in Africa. However, the rate of development and spread of amodiaquine resistance is unknown and cross-resistance with chloroquine may be a limiting factor for long-term efficacy. In addition, amodiaquine toxicity following repeated doses requires further evaluation. In clinical trials of around 960 patients, amodiaquine as monotherapy or combined with 3 days of artesunate was well tolerated. There was no evidence of significant hepatotoxicity. However, it is not yet known whether hepatotoxicity may develop after repeated treatments.

2.3 Potential combinations under consideration or trial with drugs that are not yet available

Table 22 shows the status of combinations in this category.

Table 22. Status of potential combinations under consideration or trial with drugs that are not yet available

Combination	Status
Chlorproguanil–dapsone (Lapdap) (323–325)	Multicentre phase III trial of Lapdap under way in Gabon, Kenya, Malawi, Nigeria and United Republic of Tanzania. Launch likely in early 2002.
Chlorproguanil–dapsone + artesunate (Lapdap Plus)	Phase I and II trials of Lapdap + artesunate due to start late 2001
Pyronaridine+ artemisinin derivative	Pyronaridine previously marketed in China (well tolerated and effective against CQ-resistant P. falciparum). Phase II trials in China with pyronaridine + dihydroartemisinin, artemether and artesunate showed no recrudescence, no severe adverse effects and gametocyte clearance
Dihydroartemisinin + piperaquine + trimethoprim (Artecom®)	Produced as fixed dose combination in China. Tested in Cambodia and China (clinical trials)
Dihydroartemisinin + piperaquine + trimethoprim + primaquine (CV8)	In Viet Nam, a 28-day trial showed efficacy of > 95%. Being introduced as first-line treatment in southern and central Viet Nam

CQ, chloroquine.

Chlorproguanil-dapsone (Lapdap)

This is a fixed-ratio synergistic drug association that has been shown to be efficacious in field trials in patients whose *P. falciparum* infections have failed to respond to sulfadoxine–pyrimethamine, since parasites with the triple dhfr mutation retain sensitivity to Lapdap. However, it is likely that it will not be effective against parasites with a quadruple dhfr mutation. The half-life is much shorter than that of sulfadoxine–pyrimethamine and a 3-day treatment is required. As both chlorproguanil and dapsone are rapidly eliminated, the combination is likely to exert a small selection pressure. Multicentre phase III trials are under way in Africa and preclinical safety testing is at an advanced stage. The combination is expected to be available in early 2002.

Chlorproguanil-dapsone-artesunate (Lapdap plus)

Phase I and phase II trials with Lapdap plus artesunate are due to start late 2001.

Pyronaridine-artemisinin derivative

This is being developed as a fixed combination. The rate of development of resistance was high in the mouse model. If a dosage regimen can be designed with a maximum of three daily doses, this may become a practicable ACT regimen.

Dihydroartemisinin-piperaquine-trimethoprim (Artecom®)

This has advantages over mefloquine plus artesunate. It is cheaper, has fewer adverse effects, and is available as a co-formulated tablet. Piperaquine has a short half-life.

Dihydroartemisinin-piperaquine-trimethoprim-primaquine (CV8)

This is the co-administration of primaquine and Artecom®.

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Annex 1

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Annex 2

Guidance on the selection of drugs for national antimalarial treatment policies

Introduction

This Annex uses the information summarized in earlier sections to provide guidance on the selection of drugs for use in national antimalarial treatment policies. It considers drugs for first- and second-line treatment of uncomplicated malaria and for severe malaria in infants, children under 5 years, older children, adults and pregnant women. Each possible drug is assessed according to its efficacy, dosage regimen (which influences adherence), cost and adverse effects. Key considerations for the choice of drugs and how best to use them are described. Six scenarios covering some of the major epidemiological and socioeconomic settings and drug resistance patterns are discussed. They do not cover every possible setting, but provide examples of the process of selecting options. Final decisions are the responsibility of policy-makers at country level.

Before introducing artemisinin-derivative combination therapy, a strategy needs to be developed. Decisions on which drugs to combine may follow the principle of selecting a combination of two short half-life drugs in areas of high transmission and a combination of a drug with a short half-life with one with a either a short or long half-life in areas with low transmission.

Drug developers should be encouraged to develop fixed and slow-release formulations of short half-life drugs with the aim of providing single-dose treatments.

In all the scenarios, monitoring of drug efficacy at least every two years is essential. When new polices are formulated, it is necessary to plan for their integration into existing health programmes, to liaise with the Integrated Management of Childhood Illness Programme and to institute training programmes at all levels of the health care system. Home treatment is fundamental to the success of an antimalarial treatment policy, and efforts aimed at improving compliance and reducing cost must be made. Health and diagnostic services must be strengthened to allow rational implementation of the policy and rational use of the recommended drugs.

Affordability is a major consideration for countries in choosing which drugs to recommend. In the absence of adequate resources, the best possible drugs sometimes have to be passed over for cheaper, possibly less effective drugs. This Annex therefore considers the selection of drugs in the face of economic constraints and how the choice would be influenced if increased funding was available.

Scenario 1

A country where chloroquine is the first-line treatment, but levels of resistance are high, and resistance has developed quickly to sulfadoxine–pyrimethamine in neighbouring countries when introduced as first-line treatment.

Current situation: *the currently recommended first- and second-line treatments are chloroquine and sulfadoxine–pyrimethamine respectively. The frequency of clinical failures following chloroquine treatment has become unacceptable. Neighbouring countries have an increasing incidence of sulfadoxine–pyrimethamine failures after a short period of use. There are reports of amodiaquine toxicity. The available affordable treatments are chloroquine,*

amodiaquine, sulfadoxine–pyrimethamine and quinine. Artemisinin and derivatives, mefloquine and halofantrine are all available in the private sector. Quinine is used in the district hospital to treat malaria cases in pregnant women. The Malarone® Donation Program is active. HIV prevalence at antenatal clinics is 20–30% in urban centres and 6–25% in rural areas.

This scenario is typical of several African countries in 2000. Actual levels of chloroquine resistance vary from country to country and even within countries. Resistance tends to be higher in East and southern African countries than in West Africa, but there is resistance in many West African countries. All countries need to collect efficacy data and review options continuously to ensure the best treatment. The scenario is also relevant to some other countries in Asia and South America. The antimalarial drug options are summarized in Table A2.1 and proposed treatments are set out in Table A2.2

Table A2.1—Assessing the antimalarial drug options in Scenario 1

Drug	Efficacy	Probable adherence	Cost	Comments
Chloroquine	Unacceptable	Good (once daily for 3 days)	Low	
Sulfadoxine–pyrimethamine	Acceptable at present, but may not last	Very good (single dose) but not antipyretic	Low	
Amodiaquine	No data; likely to be better than CQ, but cross-resistance may shorten useful therapeutic life	Good (once daily for 3 days – same schedule as CQ)	Low	Saftety concerns, not confirmed where used in monotherapy
Mefloquine	Likely to be high	Very good (1 day)	High	Long half life may select resistance
Halofantrine	Likely to be high	Good (2 days)	High	Severe cardiotoxicity, not recommended in national treatment policies
Quinine	High	Poor (7 days)	High	
Artemisinin combinations	High	Fixed combinations unknown; non-fixed combinations may be poor	Moderate to high	
CQ/SP combination	No data	Good (3 days)	Low but double current cost	
Atovaquone–proguanil	Likely to be high	Good (3 days)	Very high	Not recommended in young children and pregnant women

CQ, chloroquine; SP, sulfadoxine–pyrimethamine

Table A2.2—Proposed antimalarial treatment in Scenario 1

Indication	Proposed drugs	
	under current constraints	if increased funding available
First line	CQ + SP	Artesunate (3 days) + SP
Second line	Amodiaquine	Artemether–lumefantrine
Severe malaria	Quinine	Quinine or artemether or artesunate
Pregnant women	CQ + SP	Artesunate + SP
Children < 5 years	CQ + SP	Artesunate + SP

CQ, chloroquine; SP, sulfadoxine–pyrimethamine

First-line treatment

Sulfadoxine–pyrimethamine alone is less desirable for first-line treatment, as widespread use in areas with existing resistance may compromise future antifolate combinations. Given the high prevalence of HIV infections, if large-scale use of prophylactic cotrimoxazole will be implemented, there is theoretical risk that this may contribute to shortening the useful therapeutic life of sulfadoxine–pyrimethamine and other antifolates for malaria treatment. These patients need a different first-line antimalarial treatment, other than SP.

The combination of chloroquine and sulfadoxine–pyrimethamine is a possible consideration as first-line treatment, as the regimen requires the addition of a second drug, which changes health messages only slightly from the traditional chloroquine messages. Furthermore, chloroquine may alleviate initial clinical symptoms while sulfadoxine–pyrimethamine may clear parasites and give a sustained response. The combination may be given during pregnancy for treatment of malaria cases. It is important to note, however, that there is little evidence on the efficacy of this combination, so data collection should be a priority. This option cannot be administered to infants < 3 months.

Other indications

Amodiaquine may be considered as an option for second-line treatment, but again data on efficacy are needed. Quinine may be considered as the third-line drug for treatment of uncomplicated malaria and for treatment of severe malaria. Rectal artesunate is an option as an emergency pre-referral treatment and for improving community management of severe malaria, but its use must be accompanied by community education on the recognition of severe malaria symptoms.

The choice for intermittent treatment in pregnancy is sulfadoxine–pyrimethamine.

For all options, drug efficacy must be monitored closely and compared with drugs currently in use before and after the policy is implemented. The efficacy of chloroquine plus sulfadoxine–pyrimethamine, sulfadoxine–pyrimethamine alone, and amodiaquine must be determined as a priority using standard methods.

With increased funding

If financial constraints were removed, the options would be different. The options available are the co-formulated combination of artemether and lumefantrine, atovaquone–proguanil and

mefloquine. Mefloquine has a long half-life, which may produce a rapid selection of resistant parasites if used as a monotherapy. Under the definitions of the current donation programme, the use of atovaquone–proguanil (Malarone®) is restricted to third-line treatments of uncomplicated malaria. Artemether-lumefantrine may be considered as a suitable option for second-line treatment, but, before incorporation into treatment policy, it must be pilot tested under local conditions. A combination of artesunate with an existing drug may be an option for first-line therapy. Partner drugs may be sulfadoxine–pyrimethamine or amodiaquine. As above, quinine or artemether or artesunate may be used for severe malaria, with artesunate rectal suppositories for community pre-referral treatment of severe disease.

Health system

If more expensive drugs are introduced, it will be essential to strengthen health services to ensure adequate control of drugs, and to promote administration on the basis of confirmatory laboratory diagnosis to limit unnecessary use.

West Africa

In areas of West Africa where chloroquine resistance is emerging but resistance levels do not indicate that immediate change is required, close vigilance is necessary to ensure that treatment policy can be adapted rapidly if mortality due to ineffective treatment rises. Several options may be available in this case:

- Change the first-line drug to sulfadoxine–pyrimethamine; however, experience from East Africa suggests that the latter has a limited useful therapeutic life.
- Add sulfadoxine–pyrimethamine to the standard chloroquine regimen to improve therapeutic efficacy and possibility to extend the useful therapeutic life of both drugs. This would be more expensive and will double the current drug cost.
- Continue with chloroquine, but accelerate studies on alternative therapies such as combinations with artemisinins so that when resistance levels are higher, a replacement option is ready.
- Introduce artemisinin-derivative combinations with chloroquinine even with the currently low level of chloroquine resistance, if resources allow, in order to prolong the useful life of chloroquine and to discourage use of artemisinin-derivatives as monotheraphy.

Scenario 2

A country where data suggest that chloroquine and sulfadoxine–pyrimethamine are ineffective.

Current situation: *The currently recommended first- and second-line treatments are chloroquine and sulfadoxine–pyrimethamine respectively. The frequency of clinical failures following chloroquine treatment has become unacceptable. Data from resistance monitoring sites also indicate unacceptable rates of clinical failure with sulfadoxine–pyrimethamine. Efficacy varies in different parts of the country. The available affordable treatments are chloroquine, amodiaquine, sulfadoxine–pyrimethamine and quinine.*

This is the scenario facing many countries in East and southern Africa, where chloroquine can no longer be used, and there are reservations about changing to sulfadoxine–pyrimethamine because of emerging resistance. The antimalarial drug options are summarized in Table A2.3 and proposed treatments are set out in Table A2.4.

Table A2.3—Assessing the antimalarial drug options in Scenario 2

Drug	Efficacy	Probable adherence	Cost	Comments
Chloroquine	Unacceptable	Good (once daily for 3 days)	Low	
Sulfadoxine–pyrimethamine	Variable, not acceptable in some areas	Very good (single dose) but not antipyretic	Low	
Amodiaquine	Likely to be better than CQ, but cross-resistance may shorten useful therapeutic life	Good (once daily for 3 days – same schedule as CQ)	Low	Saftety concerns, not confirmed where used in monotherapy
Mefloquine	Likely to be high	Very good (1 day)	High	Long half life may select resistance
Halofantrine	Likely to be high	Good (2 days) but not as easy as SP	High	Severe cardiotoxicity, not recommended in national treatment policies
Quinine	High	Poor (7 days)	High	
Artemisinin combinations except artemether–lumefantrine	High	Non-fixed combinations may be poor	Moderate to high	
Artemether–lumefantrine	High, efficacy of 4-dose regimen lower than 6-dose in Thailand, but high in semi-immune subjects	Unknown: 4–6 doses (3 days and co-formulated but more than one dose per day)	High	
CQ + SP combination	No data	Good (3 days) Good (3 days)	Low but double current cost	
Atovaquone–proguanil	Likely to be high		Very high	Not recommended in young children and pregnant women

CQ, chloroquine; SP, sulfadoxine–pyrimethamine

Table A2.4—Proposed antimalarial treatment in Scenario 2

Indication	Proposed drugs	
	under current constraints	if increased funding available
First line	Data on efficacy of alternatives needed. Options include amodiaquine (AQ; 30 mg/kg) where AQ resistance is < 5% ; AQ + SP combination where AQ resistance > 5%; AQ + artesunate where there is SP resistance.	AQ–artemisinin derivative, co-packaged, (SP + artesunate, co-packaged)
Second line	Quinine + SP	Artemether–lumefantrine
Severe malaria	Quinine	Quinine or artemether or artesunate
Pregnant women	Q + SP after 1st trimester, AQ +SP or artesunate + SP where there is AQ resistance.	First-line Q + SP, second-line Art + SP
Children < 5 years	Same as adults	Data needed on artemether–lumefantrine in young children

AQ, amodiaquine; Q, quinine; SP, sulfadoxine–pyrimethamine

First-line treatment

This scenario highlights the problem of countries that need to change immediately but do not have adequate data on alternatives. It also raises the question of whether it is advisable to have different recommendations in different parts of a country on the basis of the different levels of resistance recorded. The functioning and level of decentralization of the health services influences this decision.

One option would be to use sulfadoxine–pyrimethamine as an interim measure where chloroquine resistance is known to be high, while data on alternatives are collected. However, the costs of introducing a new drug (for guidelines, training, drug supply and distribution) are high and may not be justified unless the drug is going to be used for some years.

Amodiaquine is a favoured option, but there are a number of points to consider:

- It could be used alone or in combinations.
- Perceptions of toxicity may limit acceptability to prescribers.
- There are concerns about efficacy in view of cross-resistance with chloroquine (and possibly with lumefantrine and halofantrine).
- Regarding toxicity, there could be a concern about the theoretical potential for bone marrow suppression with the amodiaquine plus sulfadoxine–pyrimethamine combination.

Artemether–lumefantrine has not completed phase IV trials and there are limited data about its use in children. Its use will need to be re-evaluated when more data are available.

Health system

The emergency action (interim policy) can be used as an opportunity for assessing attitudes and practices and to develop an essential package for malaria treatment. Antenatal care should be improved. HIV infections in pregnant women are likely to be high, and insecticide-treated mosquito nets should be made accessible to this risk group.

Scenario 3

A new refugee camp where several nongovernmental organizations are operating.

Following a coup in the neighbouring country, refugees have flooded across the border into an area of chronic-phase emergency. Many of the incoming refugees are from highland areas, where malaria transmission is low, while others come from lowland high-transmission areas.

About 50% of malaria infections are P. falciparum and 50% P. vivax. Within 2 weeks there is a sharp rise in severe illness in all the camps, especially among pregnant women and children under 5 years of age, and this is thought to be due to malaria. The local district hospital sends its staff to try to help, but has limited supplies of chloroquine, their first-line drug. Limited testing shows that P. falciparum is resistant to chloroquine, sulfadoxine–pyrimethamine and decreased susceptibility to quinine. No microscopic species diagnosis is possible, since laboratory facilities are poor, but tented laboratories are planned as soon as practicable.

The United Nations and five nongovernmental organizations arrive to set up health services in the camps. One nongovernmental organization brings artesunate and sulfadoxine–pyrimethamine for combination treatment, another brings sulfadoxine–pyrimethamine, believing that a 3-day treatment with artesunate will not be feasible, another follows the local protocol of chloroquine, and a fourth brings a new drug to test.

The national malaria control programme manager calls a meeting to consider whether there is a need for a special protocol in view of the difficult circumstances. The government has already stated that it cannot afford to provide expensive combinations to all the regions and is reluctant to recommend combination therapy as the national first-line treatment.

Malaria in complex emergencies contributes significantly to the global malaria burden, and raises many issues, as reflected in this scenario. The antimalarial drug options are summarized in Table A2.5 and proposed treatments are set out in Table A2.6.

Table A2.5—Assessing the antimalarial drug options in Scenario 3

Drug	Efficacy	Probable adherence	Cost	Comments
Chloroquine	Resistance reported, but data limited	In emergencies even 3-day treatment may be difficult	Low	
Sulfadoxine–pyrimethamine	Resistance reported, but data limited	Very good (single dose) but not antipyretic	Low	
Amodiaquine	Likely to be better than CQ, but cross-resistance may shorten useful therapeutic life	In emergencies even 3-day treatment may be difficult (same schedule as CQ)	Low	Saftety concerns, not confirmed where used in monotherapy
Mefloquine	Likely to be high	Very good (1 day)	High	Long half life may select resistance
Quinine	High	Poor (7 days)	High	
Artemisinin combinations (except artemether–lumefantrine)	High	Poor; non-fixed combinations may be a problem	Moderate to high	
Artemether–lumefantrine	High, efficacy of 4-dose regimen lower than 6-dose in Thailand, but high in semi-immune subjects	Poor, 3 days and co-formulated, but more than one dose per day	High	
CQ/SP combination	No data	In emergencies even 3-day treatment may be difficult	Low but double current cost	
Atovaquone–proguanil	Likely to be high	In emergencies even 3-day treatment may be difficult	Very high	Not recommended in young children and pregnant women

CQ, chloroquine; SP, sulfadoxine–pyrimethamine

Table A2.6—Proposed antimalarial treatment in Scenario 3

Indication	Proposed drugs	
	under current constraints	if increased funding available
First line	Artesunate + SP or artesunate + amodiaquine With laboratory: treat vivax malaria with chloroquine	AQ + artemisinin derivative, co-packaged (SP + artesunate, co-packaged)
Second line	Quinine (and antibiotic)	P. falciparum: artemether–lumefantrine or atovaquone–proguanil P. vivax: chloroquine
Severe malaria	Quinine	Quinine or artemisinin derivative
Pregnant women	Q + SP after 1st trimester, AQ +SP or artesunate + SP where there is AQ resistance	First-line Q + SP, second-line Art + SP
Children < 5 years	Same as adults	Data needed on artemether-lumefantrine in young children

First-line treatment

The choice of first-line treatment is based on availability of drugs (no amodiaquine), problems of follow up for primaquine, lack of confirmed diagnosis, possibilities of drug resistance and the proportion of *P. vivax* infections.

Other indications

For severe disease, intramuscular quinine is recommended (unless there are other reasons for needing infusion) because quinine resistance is unlikely, and, even if there is some resistance, quinine will work as initial rescue therapy. Susceptibilit to quinine should be checked. Quinine is easily available, nongovernmental organization physicians will be familiar with it, and it is in line with national policy.

For second-line treatment, quinine and an antibiotic are suggested because of reported decrease in susceptibility to quinine. Tetracycline should not be used in pregnant women and children under 8 years of age.

Health system

The first step is to establish whether the increase in cases is a malaria problem. Diagnosis for case management will initially be clinical, but, when tented laboratories are in place, thick films can be used. Dipsticks may have a limited role, as it is only possible to distinguish between *P. vivax* and *P. falciparum* with more expensive products.

Coordination is essential, in particular someone is needed to coordinate activities among agencies and the Ministry of Health of the country. All agencies should follow a common policy. New experimental drugs should not be tested on refugees.

Chemoprophylaxis for expatriates

If there is intense transmission, chemoprophylaxis is recommended for international travellers in combination wih mosquito bites prevention. Options include doxycycline, mefloquine, atovaquone-proguanil and primaquine (United States Food and Drug Administration approval has not yet been granted for this).

Impact on local community

Should the policy be different for local and refugee populations? This could lead to huge influx of local inhabitants seeking treatment, could exert selection pressure, which will affect the local population, and may not be sustainable in chronic emergencies. However, the national policy may be appropriate for a semi-immune local population, but not for non-immune refugees, and special measures may be needed to contain potential epidemics. Decisions should be made in dialogue with the national government and the malaria programme manager.

Monitoring is important and should include in vivo resistance testing and rapid assessment of treatment-seeking behaviour, leading to development of an information, education and communication intervention to promote early diagnosis and treatment.

Scenario 4

A country in South America.

P. vivax is responsible for 70% of all malaria infections. The currently recommended first-line treatment for uncomplicated malaria is chloroquine. Results in the northern region of the country showed no resistance to chloroquine, which was interpreted as no need to change the national first-line antimalarial treatment policy. However, there is dissatisfaction with chloroquine and a reluctance to use sulfadoxine–pyrimethamine owing to resistance to this drug in the neighbouring country. The neighbouring country reported falciparum malaria resistant to chloroquine and sulfadoxine–pyrimethamine 5 years ago and resistance to amodiaquine of 44% 2 years ago. The neighbouring country is now using mefloquine.

A village less than 5 km from the border area, with settlers from a non-malarious part of the country has a gold mining facility relatively nearby. Intense population movement is present in the region between the two countries. The frequency of clinical failures following chloroquine treatment has become unacceptable in this village and two deaths have been reported recently.

The antimalarial drug options are summarized in Table A2.7 and proposed treatments are set out in Table A2.8.

Table A2.7—Assessing the antimalarial drug options in Scenario 4

Drug	Efficacy	Probable adherence	Cost	Comments
Chloroquine	Unacceptable in some areas, high in others	Good (once daily for 3 days)	Low	
Sulfadoxine–pyrimethamine	No data but not acceptable in neighbouring country	Very good (single dose, but not antipyretic)	Low	
Amodiaquine	No data but 44% resistance in neighbouring country	Good (once daily for 3 days – same schedule as CQ)	Low	Saftety concerns, not confirmed where used in monotherapy
Mefloquine	Likely to be high	Very good (1 day)	High	Long half life may select resistance
Halofantrine	Likely to be high	Good (2 days) but not as easy as SP	High	Severe cardiotoxicity, not recommended in national treatment policies
Quinine	High	Poor (7 days)	High	
Artemisinin combinations (except artemether–lumefantrine)	High	Non-fixed combinations may be poor	Moderate to high	
Artemether–lumefantrine	High, 4-dose regimen lower than 6-dose in Thailand but high in semi-immunes.	Unknown (3 days and co-formulated) but more than one dose per day	High	Not recommended in young children and pregnant women
CQ + SP combination	No data	Good (3 days)	Low but double current cost	
Atovaquone–proguanil	Likely to be high	Good (3 days)	Very high	

Table A2.8—Proposed antimalarial treatment in Scenario 4

Indication	Proposed drugs	
	under current constraints	if increased funding available
First line	North: artesunate + mefloquine for 3 days South: mefloquine 25 mg/kg	Artemether + lumefantrine
Second line	Quinine + tetracycline	Atovaquone/proguanil + artesunate
Severe malaria	Quinine	Quinine or artemether or artesunate
Pregnant women	Quinine + clindamycin	–
Children < 5 years	Quinine + clindamycin	–

The epidemiological situation in this country requires assessment and microscopic diagnosis needs to be introduced. In vivo tests are needed to assess the efficacy of chloroquine and amodiaquine against *P. vivax* and chloroquine, amodiaquine and sulfadoxine–pyrimethamine against *P. falciparum*. Several options exist. Sulfadoxine–pyrimethamine is ineffective against *P. vivax* but can be used to treat confirmed *P. falciparum* infections, while chloroquine can be retained as the treatment of choice for *P. vivax* infections as an interim policy while awaiting results of in vivo tests. A combination of mefloquine plus artesunate, amodiaquine plus artesunate or artemether–lumefantrine may be considered as immediate options for treatment, although they are significantly more expensive than the current treatment policy of chloroquine. Without cost constraints these combinations would be more suitable. Quinine or artemether or artesunate can be used for severe malaria.

Scenario 5

A country with increasing resistance to mefloquine in some areas and low resistance to sulfadoxine–pyrimethamine in others.

The currently recommended first- and second-line treatments are mefloquine 15 mg/kg and quinine plus tetracycline respectively. The recommended first-line treatment for pregnant women and infants is quinine for 7 days. The frequency of mefloquine failures in the north-eastern part of the country has become unacceptable. The rate of emergence of mefloquine resistance has been alarmingly fast; 10–40% of patients treated with 15 mg/kg mefloquine in these regions show true recrudescence within 2 months. Pilot studies by a group of scientists using a combination of mefloquine plus artesunate in this region indicate 100% effectiveness. Sulfadoxine–pyrimethamine efficacy is high in the southern part of the country, and in these districts is the first-line therapy. However, patients in this region complain that sulfadoxine–pyrimethamine does not work, but guidelines still advise the use of this drug. The district health manager from the mefloquine district is concerned that patients from the south-east will travel to his clinics for better drugs. While there is microscopic diagnosis in the district hospital, and two health centres are using dipsticks, the health posts just use clinical classification.

This scenario is characteristic of some countries in South-East Asia, where there is high level multidrug resistance but also considerable variability in levels of resistance in different areas. The antimalarial drug options are summarized in Table A2.9 and proposed treatments are set out in Table A2.10.

Table A2.9—Assessing the antimalarial drug options in Scenario 5

Drug	Efficacy	Probable adherence	Cost	Comments
Sulfadoxine-pyrimethamine	Not acceptable in many areas, but high in some	Very good (single dose, but not antipyretic)	Low	
Mefloquine	High in some areas, unacceptable in others	Very good (1 day)	High	Long half life may select resistance
Quinine	High	Poor (7 days)	High	
Artemisinin combinations (except artemether–lumefantrine)	High	Non-fixed combinations may be poor	Moderate to high	
Artemether–lumefantrine	High, 4-dose regimen lower than 6-dose in Thailand	Unknown (3 days and co-formulated) but more than one dose per day	High	
Atovaquone–proguanil	Likely to be high	Good (3 days)	Very high	Not recommended in young children or pregnant women

Table A2.10—Proposed antimalarial treatment in Scenario 5

Indication	Proposed drugs	
	under current constraints	if increased funding available
First line	Mefloquine 25 mg/kg + artesunate (3 days) in north. Same in south or mefloquine alone	Mefloquine 25 mg/kg + artesunate (3 days), with improved diagnostics
Second line	Artemisinin derivative + doxycycline	Artemether–lumefantrine
Severe malaria	Quinine or artemisinin derivative	Quinine or artemisinin derivative
Pregnant women	Quinine 1st trimester, artemisinin combinations 2nd and 3rd trimester	Quinine 1st trimester, artemisinin combinations 2nd and 3rd trimester
Children < 5 years	Infants: quinine, children same first-line treatment as adults.	Atovaquone–proguanil + artesunate Data needed on artemether–lumefantrine in young children.

First-line treatment

Changes would increase the cost per treatment, but fewer drugs would be needed since the treatment would be effective. If *P. vivax* is present, the treatment policy will need to take this into account.

Health system

- Facilities to confirm diagnosis should be available at all treatment facilities.
- A single policy throughout the country would be the most manageable, if it can be afforded. Health system structure and the level of decentralization will determine choice.
- More efficacy information is needed.

Scenario 6

A country in Asia with multidrug resistance to *Plasmodium falciparum*.

A country that has achieved major successes in malaria control is now facing an increasing malaria problem. Transmission intensity is moderate to low. P. vivax has been the dominant malaria parasite in the past, but the incidence and proportion of P. falciparum has steadily increased, and in some districts now constitutes up to 80% of malaria infections. In these districts up to 70% of infections have been found to be resistant to chloroquine, and a few treatment failures with sulfadoxine–pyrimethamine are reported. Chloroquine is still the first line of treatment for both species in the public sector, and sulfadoxine–pyrimethamine is used only for microscopically confirmed treatment failures. However, private practitioners prescribe sulfadoxine–pyrimethamine and even mefloquine. Deaths due to malaria, which have not been experienced for many decades, are increasing in all age groups. This has brought public pressure to bear on politicians to contain malaria.

The malaria control programme manager wants to launch a major attack in the malaria transmission foci against P. falciparum; she is convinced that P. falciparum is persisting and spreading because of drug resistance and the continued use of ineffective drugs, leading to large reservoirs of this species. Given the effects of artemisinin derivatives on gametocytes and the successful Thai-Myanmar border experience with artesunate-containing drug combinations in decreasing P. falciparum incidence, the proposal is to deploy artemether–lumefantrine together with intensive vector control activities as a crisis intervention measure to reduce drastically the reservoir of P. falciparum.

The antimalarial drug options are summarized in Table A2.11 and proposed treatments are set out in Table A2.12.

Table A2.11—Assessing the antimalarial drug options in Scenario 6

Drug	Efficacy	Probable adherence	Cost	Comments
Chloroquine	Low in areas of high *P. falciparum* incidence	Good (once daily for 3 days)	Low	
Sulfadoxine–pyrimethamine	Few treatment failures reported	Very good (single dose, but not antipyretic)	Low	
Mefloquine	Likely to be high	Very good (1 day)	High	Long half life may select resistance
Quinine	High	Poor (7 days)	High	
Artemisinin combinations (except artemether–lumefantrine)	High	Non-fixed combinations may be poor	Moderate to high	
Artemether–lumefantrine	High, 4-dose regimen lower than 6-dose in Thailand	Unknown (3 days and co-formulated) but more than one dose per day	High	
CQ + SP combination	No data	Good (3 days)	Low but double current cost	

CQ, chloroquine; SP, sulfadoxine–pyrimethamine

Table A2.12—Proposed antimalarial treatment in Scenario 6

Indication	Proposed drugs	
	under current constraints	if increased funding available
First line	Data needed on efficacy of alternatives. **Options include:**	Artesunate + SP or artesunate + mefloquine or artemether–lumefantrine
	MQ (15 + 10 mg/kg) + PQ (45 mg) or artemether–lumefantrine in high *P. falciparum* foci, CQ + SP elsewhere (not SP alone as *P. vivax* present). CQ and PQ for *P. vivax* where diagnosis possible	*P. vivax*: CQ and PQ (14 days – 30 mg or 8 weeks – 45 mg) where definite diagnosis possible
Second line	Artesunate + mefloquine in foci, quinine + SP elsewhere	Artesunate + mefloquine or artemether–lumefantrine
Severe malaria	Quinine + doxycycline or SP	Quinine or artemisinin-derivative
Pregnant women	Quinine (3 days) + SP or MQ in 2nd and 3rd trimesters	Quinine (3 days) + SP or mefloquine in 2nd and 3rd trimester
Children < 5 years	Same as non-pregnant adults	Same first-line treatment as non-pregnant adults except for artemether-lumefantrine in young children

CQ, chloroquine; MQ, mefloquine; PQ, primaquine; SP, sulfadoxine–pyrimethamine

First-line treatment

Although artemether–lumefantrine may be an option for this scenario, and could potentially reduce transmission, as most infections will be symptomatic and thus treated, there are no safety or adherence data available with this drug in this region. This combination has the advantage of being co-formulated as well as having limited previous use in the private sector.

An alternative is mefloquine combined with primaquine or artesunate. The combination of mefloquine and primaquine is inexpensive, it is a shorter treatment already registered, it is effective against *P. vivax*. The addition of artesunate to mefloquine would give rapid action and recduce gametocyte carriage rate. Mefloquine–artesunate compared to the six-dose adult artemether–lumefantrine treatment, is a shorter treatment, is already registered, is effective against vivax malaria, and can be used in pregnancy, after the first trimester.

The suggestion to use chloroquine plus sulfadoxine–pyrimethamine in the rest of the country is based on the likelihood of significant chloroquine resistance elsewhere, and the need to treat *P. vivax* as well as *P. falciparum*. When the crisis is over this new first-line treatment could be adopted for use in foci. It is less expensive than artemether–lumefantrine or mefloquine plus artesunate, but there may be problems of acceptability. However, if affordable, it would be better to continue with mefloquine plus artesunate or artemether–lumefantrine in the whole country.

Useful information to be gathered would include:

- Passive surveillance of severe adverse events following treatment.
- Monitoring therapeutic efficacy in sentinel sites.
- Retrospective monitoring of adherence to the treatment in a random subset.
- Monitoring of reported slide/confirmed malaria with weekly or monthly summaries of incidence at health centres
- Retrospective monitoring of accidental exposure to artemether–lumefantrine in pregnant women by documenting pregnancy outcomes.
- Safety and efficacy data for new combination therapies such as artemether–lumefantrine can be generated once the immediate crisis is over. These therapies can then be introduced in the national drug policy.

Vector control and distribution of insecticide-impregnated bednets should also be implemented. Rapid dipsticks can also be introduced. However, they are expensive and may not be affordable in areas with financial constraints.

Annex 3

Summary of the characteristics of common antimalarial drugs that should be considered in drug selection

Annex 3

Summary of the characteristics of common antimalarial drugs that should be considered in drug selection

Option	Effective against		Cross-resistance	Dosage and regimen	Cost (US$) per adult treatment course	Adverse effects
	P. vivax	P. falcip. resist. to				
Chloroquine	Yes		Hydroxy-chloroquine, Possibly amodiaquine, pyrimethamine, quinine	25 mg/kg chloroquine base 100 mg base is equivalent to 123 mg chloroquine hydrochloride and 136 mg sulfate) over 3 days	Tablets: 0.072 (0.062-0.08) Syrup: 0.85 (0.21-2.37) Injection: 0.54 (0.49-0.63)	Visual disturbances, GI distubances, vomiting, anorexia, cutaneous reactions transient head-aches, neuropsychiatric effects, fatigue, seizures,ruritis (in dark-skinned people), acute porphyria Rare; haematological effects, neurological disorders, some cardiovas cular effects, otic effects, myotoxicity, severe cutaneous reactions Long-term use may result in irreversible visual impairment with keratopathy and retinopathy Overdosage: cardiac arrest
Amodiaquine	Yes	CQ (partially)	Chloroquine	30 mg/kg amodiaquine base over 3 days	0.15	Nausea, vomiting, abdominal pain, bradycardia, diarrhoea, pruritis, toxic hepatitis, agranulocytosis
Sulfadoxine-pyrimethamine	No	CQ	Antifolates	Adults: 1500 mg sulfadoxine + 75 mg pyrimethamine (single dose)	0.082 (0.065-0.098)	Anorexia, GI disorders, ataxia, tremor Rare: headache, light-headedness, malaise, fatigue, irritability, insomnia, serious cutaneous reactions Very rare: Stevens.Johnson syndrome, toxic epidermal necrolysis after prophylactic administration, hepatotoxicity, vasculitis, agranulocytosis, erythroderma, thrombocy topenia, megaloblastic anaemia, leukopenia, methaemoglobinaemia
Sulfalene-pyrimethamine	No	CQ	Antifolates	Adults: 1500 mg sulfalene + 75 mg pyrimethamine (single dose) Children: sulfalene 25 mg/kg + pyrimethamine 1.25 mg/kg	0.28	As for sulfadoxine-pyrmethamine
Quinine	Active against sexual & asexual erythrocytic forms	CQ and SP (sometimes cross-resistance with CQ)	Mefloquine (rare: with 4-amino quinolines); quinine is generally effective against CQ and SP resist.	24 mg/kg daily in three divided doses for 3, 7 or 10 days, depending on area and whether used alone or in combination; usually given for 7 days when given alone	Tablets: 1.35 (1.22-1.63) Injection: 2.57 (2.21-3.0) (7 days)	CNS, GI and cardiovascular disorders related to dose, thrombocytopenia, leukopenia, agranulocytosis, pancytoenia, coagulopathy, hepatic toxicity, haemolytic-uraemic syndrome, renal failure ventricular tachycardia, anginal symptoms,severe hypotension, hypoglycaemia, cinchonism, metallic taste, dizziness, tinnitus
Quinimax (a combination of quinine, quinidine,cinchonine and cinchonidine)	As for quinine	CQ and SP	Mefloquine	As for quinine	Price not available	As for quinine
Quinidine	As for quinine	CQ and SP (sometimes cross-resistance with CQ)	Mefloquine	As for quinine	8.82	Cinchonism (tinnitus, muffled hearing, vertigo,dizziness, headache, blurred vision, GI effects) pruritis, erythematous rashes, subcutaneous or submucous haemorrhage, cardiosuppresant effect (more important than with quinine), CNS effects (dose related) severe hypotension, hypoglycaemia
Mefloquine (15 mg/kg)	Yes	4-amino-quinolones and SP combinations	Halofantrine, reduced sensitivity to quinine	Adults and children: 15 mg/kg (single dose)	2.14 (1.55-3.18)	GI effects, disturbed balance, blurred vision abnormal coordination, anxiety, dermatological events, affective disorders, CNS effects (overt psychosis, toxic encephalopathy, convulsions, hallucinations, cardiovascular effects) Rare: headache, bradycardia, rash, pruritis weakness, vertigo, sleep disturbances, nightmares cardiopulmonary arrest, transient AV block,pericarditis, cardiovascular collapse, myocardial infarction, agranulocytosis

Drug interactions	Half-life	Contraindications	Reported resistance	Formulations	Comments
Antacids or kaolin (should be given at least 4 h apart), cimetidine, rabies vaccine, metronidazole, ampicillin. Increased risk of convulsions in combination with mefloquine. May be antagonistic when used with quinine	10 days (depending on sensitivity of assay method) up to 2 months	History of epilepsy, persons with retinal or visual field changes, patients with porphyria (unless benefits outweigh potential hazard), psoriasis	Yes; P. falciparum resistant in many areas of South-East Asia, Africa, South America and Oceania P. vivax is resistant in Indonesia and Papua New Guinea	Tablets, 50 mg, 100 mg, 150 mg 300 mg base (as phosphate or sulfate) Syrup, 50 mg base (as phosphate or sulfate) in 5 ml Injection, 50 mg, 100 mg base (as phosphate or sulfate) per ml in 2-ml ampoule	Oral chloroquine phosphate is drug of choice for the treatment of uncomplicated malaria caused by P. malaria, P. ovale, susceptible strains of P. falciparum, but chloroquine-resistant strains of P. falciparum have been reported in all areas where malaria occurs except Haiti and Central America
No adverse drug interactions have been observed	10 h	Chemoprophylaxis, persons with hepatic disorders	Yes in many areas in Asia, East Africa, Papua New Guinea and the Amazon Basin	Tablets, 153,1 mg, 200 mg, (amodiaquine base as hydrochloride) Suspension (10 mg/ml amodiaquine base as HCl)	Some reports of hepatotoxicity and agranulocytosis; however, there is no conclusive evidence on toxicity when used in therapeutic doses. Concern about its cross-resistance with CQ
Drugs that interfere with folic acid metabolism, p-amino benzoic acid, other sulfonamides, cotrimoxazole, lorazepam, zidovudine, folic acid	180 h (sulfadoxine) 95 h (pyrimethamine)	Chemoprophylaxis, severe hepatic or renal dysfunction (except where benefits exceed the risk), megaloblastic anaemia caused by folate deficiency Infants < 2 months	Resistance reported in South-East Asia, Amazon Basin, East and South Africa, Bangladesh, Central & South America, Oceania and India	Tablets, 500 mg sulfadoxine, 25 mg pyrimethamine Injection 500 mg sulfadoxine, 25 mg pyrimethamine in 2.5-ml ampoule	Single-dose therapy, therefore adherence is high but risk of resistance developing rapidly owing to long half-life. Used in CQ-resistant areas
Drugs that interfere with folic acid metabolism, p-amino benzoic acid, other sulfonamides, cotrimoxazole, lorazepam, folic acid	65 h (sufalene) 95 h (pyrimethamine)	Chemoprophylaxis, severe hepatic or renal dysfunction (except where benefits exceed the risk), megaloblastic anaemia caused by folate deficiency Infants < 2 months	Resistance reported in South-East Asia, Amazon Basin, sub-Saharan Africa, Bangladesh, Oceania	Tablets, 500 mg sulfalene, 25 mg pyrimethamine	Single-dose therapy, therefore high adherence but high risk of resistance developing rapidly owing to long half-life. Used in CQ-resistant areas
Mefloquine, cardiac glycosides, astemizole, flecainide, terfenadine, antacids containing aluminium, cimetidine used with chloroquine may be antagonistic, neuromuscular blocking agents, anticoagulants, drugs that increase urinary pH	10-12 h	Studies found no evidence of oxytoxic effects when used for falciparum malaria in 1st trimester of pregnancy	Countries in southern Asia east of Bangladesh, several African countries on the Gulf of Guinea, some reports in E. Africa	Tablets 200 mg, 300 mg base (as sulfate), Injection 150 mg, 300 mg base (as dihydro-chloride) per ml in 2-ml ampoule	Used for uncomplicated malaria in multidrug-resistant areas where P. falciparum does not respond to CQ, SP combinations and mefloquine; travellers returning to non-endemic areas who develop malaria; patients with uncomp. malaria repeatedly vomiting; 2nd-line treatment for 1st line treatment failures or in hypersensitivity to sulfonamides (used in combination)
As for quinine	As for quinine	As for quinine	As for quinine	Tablets 125 mg, 500 mg (100 mg: 59.3 mg quinine, 1.6 mg quinidine, 0.4 mg cinchonine, 0.4 mg cinchonidine base) Injection, 100 mg, 200 mg,	Limited studies show no significant difference between therapeutic efficacy of quinimax and quinine
Neuromuscular blocking agents, cholinergic and anticholinergic agents, alkalinizing agents, thiazide diuretics, some antacids, cimetidine, coumarin anticoagulants, anticonvulsants phenothiazines, reserpine, cardiovascular drugs, other antiarrhythmic agents	10-12 h	Patients with AV junctional or idioventricular pacemaker, left bundle branch marked widening of the QRS complex, patients with ectopic impulses and rhythms due to escape mechanisms, cardiac glycoside-induced AV conduction disorders. Not recommended for use in pregnancy. Use with extreme caution in nursing women	Rarely reported in falciparum malaria	400 mg per ml Tablets 200 mg base (as sulfate)	Not recommended for routine treatment of uncomplicated malaria. Useful for treatment of parenteral treatment of severe and complicated malaria and may be used instead of quinine in patients with uncomplicated malaria requiring an initial dose of parenteral therapy
Cardioactive agents, antidepressants, quinine, quinidine, primaquine, halofantrine, ampicillin, tetracycline, metoclopramide, valproic acid. Human diploid cell rabies vaccine (HDCV) should be administered by intramuscular not intradermal route	10-40 days (shorter in children and pregnant women)	Cardioactive drugs, actvities requiring fine coordination, history of neurological or psychiatric disease, treatment with mefloquine in previous 4 weeks. Studies show that use for treatment or prevention in 2nd or 3rd trimester is not associated with adverse outcome	Yes, Thail-Cambodian and Thai-Myanmar borders (sporadic reports in South America (Brazil, Guyana and French Guyana), Asia, Africa and Middle East)	Tablets 250 g base (as hydrochloride)	Used for P. falciparum infection resistant to CQ or SP combinations, recommended for chemoprophylaxis for travellers to areas with risk of CQ-resistant falciparum malaria

Option	Effective against		Cross-resistance	Dosage and regimen	Cost (US$) per adult treatment course	Adverse effects
	P. vivax	P. falcip. resist. to				
Mefloquine (25 mg/kg)	Yes	As for mefloquine (15 mg/kg)	As for mefloquine (15 mg/kg)	25 mg/kg in two divided doses given 12 h apart	3.22 (2.33-4.77)	As for mefloquine (15 mg/kg)
Halofantrine	Yes	CQ, SP quinine	Mefloquine	Adults and children > 1 year: 24 mg/kg base in three divided doses at 6-h intervals (manufacturer recommends a second course of therapy one week after first treatment)	Tablets: 4.75 Syrup: 0.28	Nausea, abdominal pain, diarrhoea, pruritis, skin rashes, prolongation of PR and QT interval, serious ventricular dysrrythmias, individual report of cardiac arrest and torsades de pointes, intravascular haemolysis, convulsive seizures, compromising renal function
Artemether	Yes	CQ, SP quinine		4 mg/kg loading dose on day 1, then 2 mg/kg once daily for 6 days	Tablets: 4.20 (China) Injection: 8.8 (China)	GI effects, itching, drug fever rare: abnormal bleeding and dark urine, minor cardiac changes cardiotoxicity, neurotoxicity in animals (in vitro studies have shown that dihydroartemisinin is neurotoxic)
Artemisinin	Yes	CQ, SP quinine		20 mg/kg in divided dose on day 1, then 10 mg/kg once daily for 6 days	Tablets: 2.10 (Viet Nam)	As for arthemether
Artesunate	Yes	CQ, SP quinine		4 mg/kg loading dose on day 1, then 2 mg/kg once daily for 6 days	2.16 (1.98-2.33) Injection: 11.2	As for artemether
Dihydroartemisinin	Yes	CQ, SP quinine		Adults: 4 mg/kg on day 1 followed by 2 mg/kg daily for 6 days	Price not available	As for artemether
Artelinic acid	No data available					
Primaquine	Yes			Radical treatment of P. vivax and P. ovale: 0.25 mg/kg daily for 14 days (outside SE Asia & Oceania); 0.50 mg/kg daily for 14 days or 0.75 mg/kg weekly for 8 weeks (SE Asia & Oceania); gametocytocidal: 0.75 mg/kg single dose	Antirelapse: 0.06-0.24 0.04-3.15)	GI effects, cramps, weakness, haematological disorders, suppression of myeloid activity, methaemoglobinaemia, haemoglobinaemia, agranulocytosis, granulocytopenia, hypertension and cardiac arrhythmia intravascular haemolysis, haemoglobinaemia Rare: headache, interference with visual accomodation and pruritis
Doxycycline	No	Used in combination with quinine in areas of reduced quinine susceptibility		Treatment in adults: 100 mg/day with quinine (3/7 days); 200 mg/day with mefloquine or artesunate (5 days); not used alone for treatment	0.08-0.11 (0.06-0.21)	GI effects, anorexia, phototoxic reactions, transient depression of bone growth discoloration of teeth and enamel hypoplasia (permanent), hypersensitivity reactions (rare), pre-existing renal insufficiency may be aggravated, acute renal failure, hepatic and haematologic effects (rare), oesophageal ulceration (rare: stomatitis, glossitis, dysphagi sore throat, pancreatitis, anogenital inflammation, black hairy tongue, cardiac overgrowth)
Tetracycline	Yes	Used in combination with quinine in areas of reduced quinine susceptibility		Adults and children > 8 years: 250 mg 4 times daily in combination with quinine; not used alone for treatment	0.14-0.20 (0.12-0.25)	GI effects, depletion of normal bowel flora phototoxic reactions, porphyria-like skin changes, pigmentation of nails
Proguanil	Yes		Pyri-methamine	Not used alone for treatment		Mouth ulceration
Dapsone	No			Not used alone for treatment		Fever, convulsions, anaemia, GI effects, headache, mouth ulcers, anorexia, neuropathy allergic dermatitis, severe anaemia, leukopenia
Atovaquone-proguanil	No	CQ, SP, halofantrine, mefloquine, amodiaquine		Adults: 1 g atovaquone + 400 mg proguanil (4 tablets) as a single dose for 3 days Children 11-20 kg: 62.5/25 mg daily (1 paediatric tablet); 21-30 kg: 2 tablets; 31-40 kg: 3 tablets; >40 kg: 1 adult tablet daily	42	Headache, abdominal effects, anorexia, coughing

Drug interactions	Half-life	Contraindications	Reported resistance	Formulations	Comments
As for mefloquine (15 mg/kg)	10-40 days	As for mefloquine (15 mg/kg)	As above	Tablets, 250 g base (as hydrochloride)	As above
Quinine (increased risk of cardiac effects), mefloquine (increased risk of cardiac effects), sparfloxacine	1-6 days	Pre-existing cardiac disease, history of or use of drugs that prolong QT interval, age < 1 year, pregnancy treatment with mefloquine during preceding 3 weeks, breastfeeding, family history of prolongation of QT intervals.	No	Tablets, 250 mg (hydro-chloride) Paediatric suspension, 100 mg/5 ml	Restricted to the treatment of acute multidrug-resistant falciparum infections; not recommended for standby treatment
No pharmacological interactions with other drugs have been identified	4-11 h (11-12 h or dihydro-artemisinin following artemether administration)	Not recommended during first trimester. Can be used during the 2nd or 3rd trimester	There have been no reports of clinical resistance to artemisinin drugs	Oily solution for injection 80 mg in 1-ml ampoule, 40 mg/ml (paed) Capsules, 40 mg Composite tablets, 50 mg	Uncomplicated multidrug-resistant falciparum malaria. WHO recommends that artemisinin compounds should be administered in combination with mefloquine for a minimum of 3 days. If used alone, treatment should be for a minimum of 7 days. Main advantage is speed of action. Caution with prolonged repetitive doses owing to neurotoxicity
As for artemether	4-11 h (11-12 h for dihydro-artemisinin following artemether administration)	As for artemether	There have been no reports of clinical resistance to artemisinin drugs	Tablets, 250 mg Suppository 100 mg, 200 mg 300 mg, 400 mg, 500 mg	As for artemether
As for artemether	4-11 h (11-12 h for dihydro-artemisinin following artemether administration)	As for artemether	There have been no reports of clinical resistance to artemisinin	Tablets, 50 mg, 200 mg Powder for injection 60 mg of anhydrous artesunate in 1 ml Suppository 100 mg Rectocap 200 mg	As for artemether
As for artemether	40 min	As for artemether	As for artemether	Tablets, 20 mg, 60 mg, 80 mg Suppositories, 80 mg	As for artemether
	No data available	No data available	No data available	-	-
Any other drugs that may induce haematological disorders, quinacrine, quinine (reduces plasma concentrations of primaquine)	5 h (3.7-9.6 h)	Children < 4 years (risk of haemolysis) active rheumatoid arthritis, lupus erythematosus, conditions that pre-dispose to granulocytopenia, patients with G6PD deficiency. Contraindicated in pregnancy owing to risk of haemolysis in fetus	Resistance occasionally reported to primaquine only.Vivax malaria resistant to primaquine mainly due to sub-therapeutic doses.	Tablets, 5.0 mg, 7.5 mg, 15.0 mg base as diphosphate	Used in antirelapse treatment in P. viva and P. ovale infections. Used as a gametocytocidal drug with an effective blood schizonticidal drug
Oral anticoagulants, halogenated agents, drugs affecting GI pH, anti-infective agents, products containing kaolin, pectin or bismuth, barbiturates, phenytoin, carbamazepine, oral contraceptives (caution: drugs with divalent or trivalent cations, antacids with Ca, Mg, Al)	14-24 h	Known hypersensitivity, age < 8 years, pregnancy, persons with hepatic dysfunctions.	Only used in combination	Capsule or tablet, 100 mg as hyclate	Used only in combination with quinine mefloquine or artesunate for treatment. Also used for chemoprophylaxis
As for doxycycline	8 h	Pre-existing severe hepatic or renal damage, age < 8 years. Not recommended for use in pregnancy	Only used in combination	Capsule or tablet, 250 mg as hydrochloride	Never used alone. Used in combination with quinine in treatment of falciparum malaria when resistance to quinine has been reported and in patients in whom SP is contraindicated
Warfarin	16 h	Areas with known resistance	Only used in combination	Tablet, 100 mg as hydrochloride	Used in combination with chloroquine for chemoprophylaxis. Used in newe combinations for treatment (see below)
No adverse drug interactions have been observed		Patients with liver failure Not recommended for use in pregnancy	Only used in combination	Tablets, 50 mg, 100 mg	Used in new combinations under development (see below)
Tetracycline, metoclopramide, rifampicin rifabutin (associated with decreased plasma concentration of atovaquone)	2-3 days (atovaquone) 12-21 h (proguanil)	Chemoprophylaxis in patients with severe renal impairment. Safety not yet established in pregnancy. Used with caution in nursing women.	No	Tablets (250 mg atovaquone/ 100 mg proguanil hydrochloride) Pediatric tablets (68.5 mg atovaquone/ 25 mg proguanil hydrochloride	Used for treatment of acute falciparum malaria in areas resistant to CQ, SP, mefloquine, halofantrine, amodaquine (also used for prevention in some countries). Co-formulated tablet

Option	Effective against		Cross-resistance	Dosage and regimen	Cost (US$) per adult treatment course	Adverse effects
	P. vivax	P. falcip. resist. to				
Pyronaridine	No			In new combination under development (see below)		Headache, dizziness, GI disorders transient ECG changes Rare: palpitations, skin rash, epigastric distress
Quinine + doxycycline	Yes	Q alone	As for quinine and doxycycline	Quinine-sensitive areas: quinine 8 mg/kg daily (3 days), doxycycline 100 mg daily (7 days) High level of resistance: quinine and doxycycline as above for 7 days (usually 7-day treatment is given)	Q sensitive areas, Q-3 + D-3 0.63 (0.55-0.84) Q-resistant areas, Q-7 + D-7 1.47 (1.3-1.66)	As for quinine and doxycycline
Quinine + tetracycline	Yes	Q alone	As for quinine and tetracycline	Quinine-sensitive areas: quinine 8 mg/kg daily (3 days), tetracycline 250 mg four times/day (5 days) High level of resistance: quinine and tetracycline as above for 7 days	Q-sensitive areas, Q-3 + T-5 0.79 (0.66-1.16) Q-resistant areas, Q-7 + T-7 1.65 (1.42-2.27)	As for quinine and tetracycline
Quinine + sulfadoxine-pyrimethamine	Yes	Q alone	As for quinine and SP	Quinine 8 mg/kg daily (3 days) 1500 mg sulfadoxine or sulfalene, 75 mg pyrimeth-amine on first day only	0.66 (0.59-0.8)	As for quinine and SP
Artesunate + mefloquine	Yes	CQ, SP, mefloquine	As for mefloquine	Single dose of 4 mg/kg for 3 days (ASU) and 15-25 mg/kg (MQ)	5.38 (4.06-7.04)	As for artesunate and mefloquine
Artemisinin + mefloquine	Almost no data		As for mefloquine	20 mg/kg in divided dose, then 10 mg/kg for 2 more days (ART) and 15-25 mg/kg (MQ)		
Artesunate + sulfadoxine pyrimethamine	Yes	CQ	As for SP above	Single dose of 4 mg/kg (ASU) for 3 days and single dose of SP	2.24 (2.05-2.43)	As for artesunate and SP
Chloroquine + sulfadoxine-pyrimethamine	Yes	CQ		CQ 25 mg/kg over 3 days, SP 25 mg/kg (S) single dose	0.154 (0.127-0.18)	As for CQ and SP
Chloroquine + sulfalene-pyrimethamine	Yes	CQ		CQ 25 mg/kg over 3 days SP: 25 mg/kg (S) single dose	0.35 (0.34-0.36)	As for CQ and SP
Artemether-lumefantrine	No	CQ, SP	As for artemether	Adults: four tablets initially then again after 8 h, then twice daily for 2 days Children: 10-14 kg, one tablet as above; 15-25 kg, two tablets as above; 25-30 kg, three tablets as above	2.5	Headache, dizziness, sleep disorders, palpitation GI disorders, skin disorders, cough, asthenia, fatigue, arthralgia, myalgia

Combinations under development

Option	Effective against		Cross-resistance	Dosage and regimen	Cost (US$) per adult treatment course	Adverse effects
	P. vivax	P. falcip. resist. to				
Dapsone-chlorproguanil	No	CQ, SP	Possibly other antifolates	Chlorproguanil 2 mg/kg, Dapsone 2.5 mg/kg	Not known (possibly < 0.50)	Fever, convulsions, anaemia, GI effects headache, mouth ulcers, anorexia, neuropathy allergic dermatitis, dapsone syndrome (rash with fever), severe anaemia, leukopenia
Dapsone-chlorproguanil + artesunate	Yes	CQ, SP		Single daily dose for 3 days	Not known	As for dapsone-proguanil and artesunate
Pyronaridine + artesunate	Yes	CQ, SP		Single daily dose for 3 days	Not known	As for pyronaridine and artesunate

Drug interactions	Half-life	Contraindications	Reported resistance	Formulations	Comments
No adverse drug Interactions have been observed	60-90 h	Not recommended for use in pregnancy or lactating women (until further studies establish safety), children < 11 kg	No	Tablets	In combination under development. Only available as single drug in China
Mefloquine, halofantrine, cardioactive agents	16 h (quinine) 15-25 h (doxycycline)	Children < 8 years Not recommended for use in pregnancy	No	As for quinine and doxycycline	Used in areas where resistance to quinine has been reported. Non-fixed dose combination.
Mefloquine, halofantrine, cardioactive agents	16 h (quinine) 8-10 h (tetra-cycline)	Children < 8 years. Not recommended for use in pregnancy	No	As for quinine and tetracycline	Used in areas where resistance to quinine has been reported. Non-fixed dose combination.
As for quinine and SP	See quinine and SP	As for quinine and SP	No	As for quinine and SP	For use in areas where parasites are SP and quinine resistant and adherence may be a problem. Non-fixed dose combination
As for artesunate and mefloquine	See artesunate and mefloquine	As for artesunate and mefloquine. Not recommended for use in 1st trimester of pregnancy	No	As for artesunate and mefloquine	Used in mefloquine-resistant areas. Non-fixed dose combination
As for artemisinin and mefloquine	See artemisinin	Not recommended for use in 1st trimester of pregnancy	No	As for artemisinin and mefloquine	Used in mefloquine resistant areas. Non-fixed dose combination
As for artesunate and SP	See artesunate and SP	As for artesunate and SP	No	As for artesunate and SP	Used in multidrug-resistant areas Non-fixed dose combination
As for CQ and SP	See CQ and SP	As for CQ and SP	No	As for CQ and SP	Used for mixed chloroquine-resistant and chloroquine-sensitive P. falciparum
As for CQ and SP above	See CQ and SP	As for CQ and SP		As for CQ and SMP	Non-fixed dose combination
No specific drug interactions have been studied	2 h (artemether) lumefantrine: 2-3 days 4-6 days (patients with malaria)	Safe use in pregnancy not yet established		Tablets, 20 mg artemether 120 mg lumefantrine	Not evaluated for treatment of severe malaria. Better absorbed in the presence of food. Fixed-dose combination

Combinations under development

Drug interactions	Half-life	Contraindications	Reported resistance	Formulations	Comments
No specific adverse drug interactions have been studied	17-33 h (dap) 20 h (chloproguanil)	Patients with liver failure, history of G6PD deficiency or intravascular haemolysis. Adequate data on pregnancy not available	Not in use yet	None yet	New fixed-dose combination for use in Africa, Middle-East and Indian sub continent. Selects parasites less readily than SP. Presence of quadruple dhfr may render it ineffective Expected to be available in 2001
No specific adverse drug interactions have been studied	17-33 h (dap) 20 h chloproguanil 4-11 h (artesunate)	Adequate data on pregnancy not Available	Not in use yet	None yet	Triple combination expected to be available in 2003
No specific adverse drug interactions have been studied	60-90 h (pyronaridine) 4-11 h (artesunate)	Not recommended for use in pregnant or lactating women until further studies establish safety	Not in use yet	None yet	New fixed-dose combination with adherence advantages, limited use thus less likelihood of early resistance Expected to be available in 2003

FOR YOUR NOTES

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Roll Back Malaria is a global partnership founded by the governments of malaria-afflicted countries, the World Health Organization, the UN Development Programme, the UN Children's Fund and the World Bank. Its objective is to halve the burden of malaria for the world's people by the year 2010 by saving lives, reducing poverty, boosting school attendance and making life better for millions of people living in poor countries, especially in Africa.

If you are interested in becoming part of the Roll Back Malaria movement, receiving the RBM newsletter and becoming part of the global success story in reducing malaria, please write to:

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